Cancer Survivorship: An Emerging Focus for Cancer Prevention and Control Efforts

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St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Overview

- Background on Cancer Survival
- Pediatric Cancers
  - Mortality
  - Second Malignancies
  - Chronic Conditions
  - Tobacco
  - Obesity
- Survivorship Research – St. Jude

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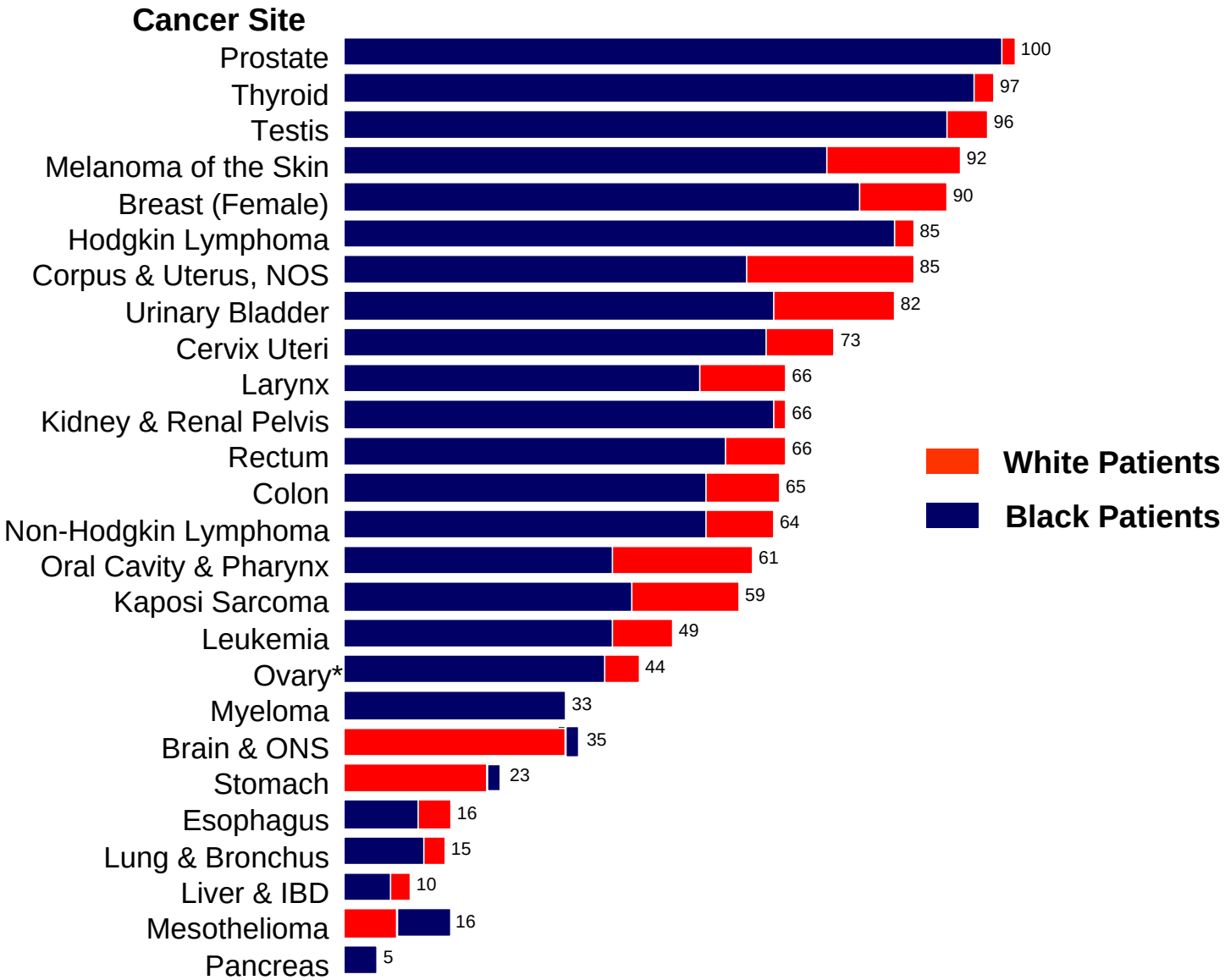
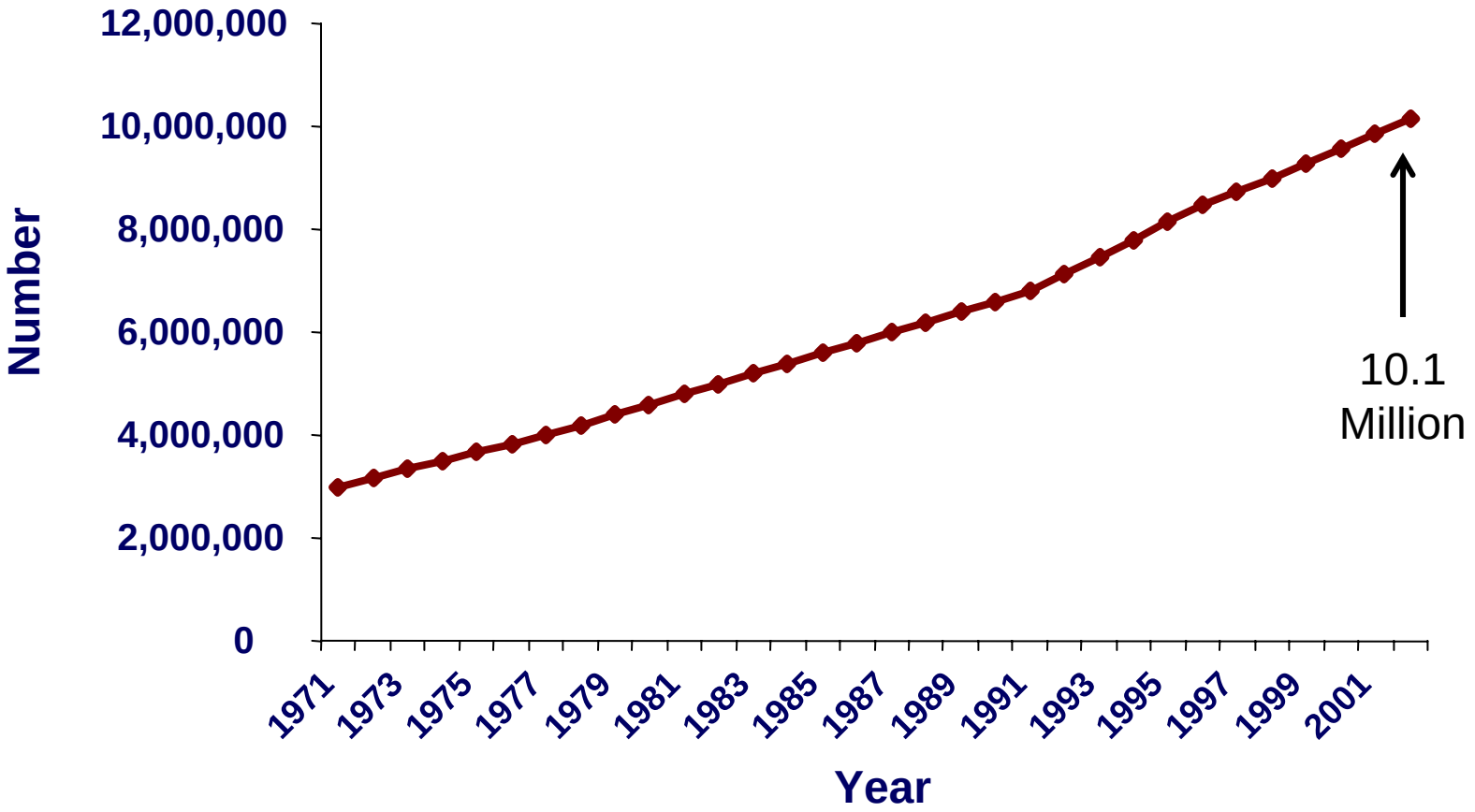
5-Year Relative Survival Rates

SEER Program, (1996-2002) Both Sexes, by Race

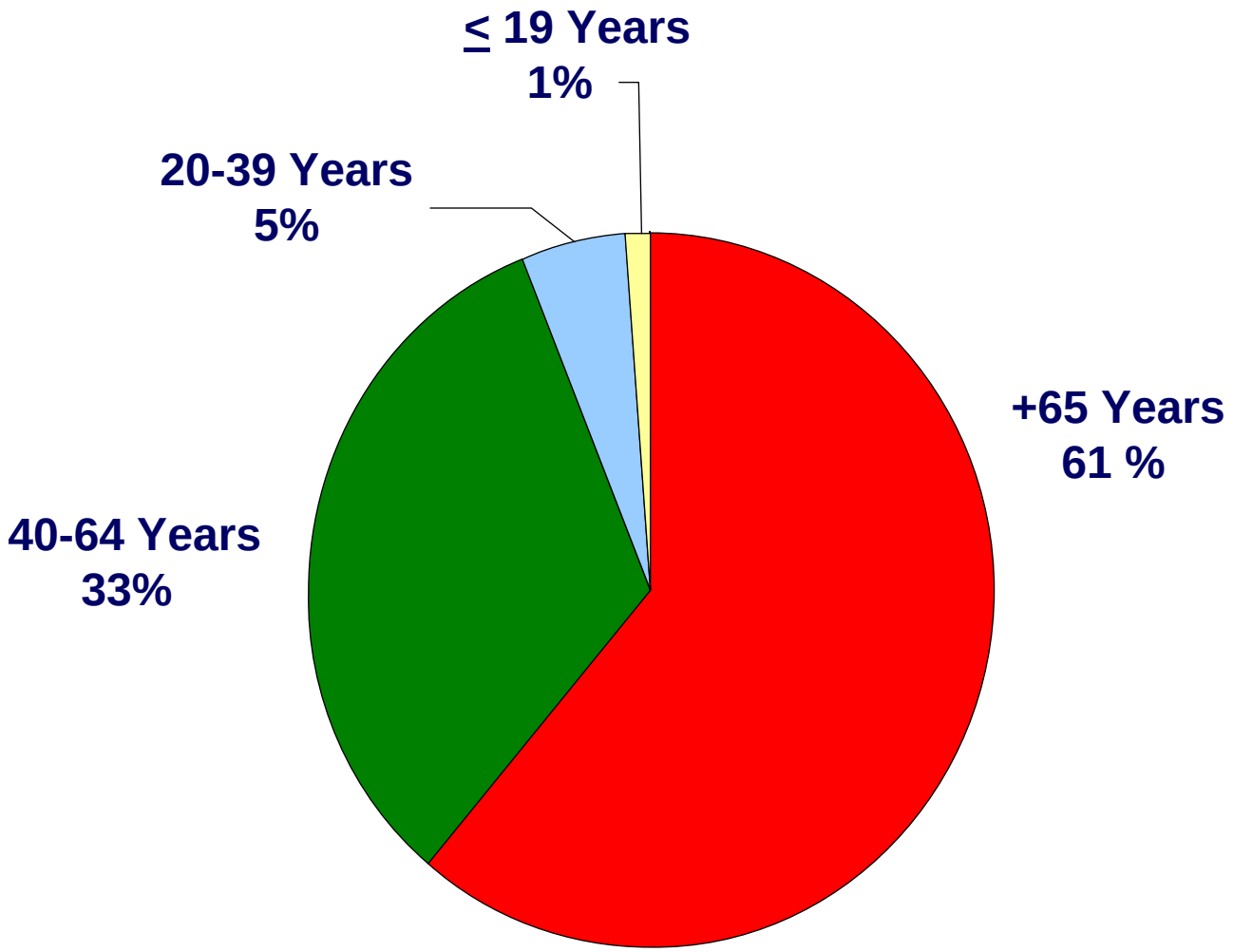


Estimated Number of Persons Alive in US Diagnosed with Cancer



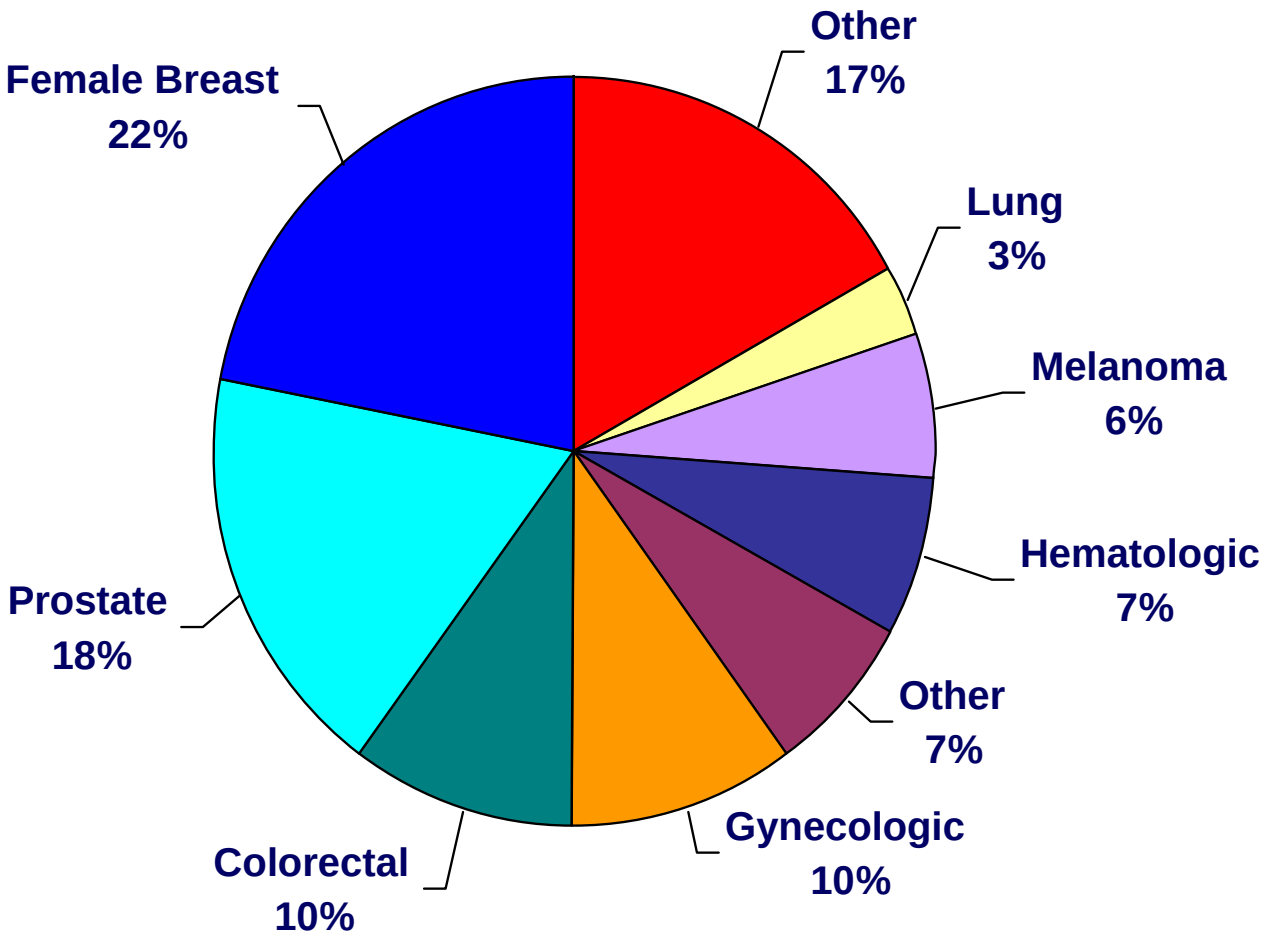
Source: SEER & NCI Office of Cancer Survivorship

Estimated Number of Persons Alive in the U.S. Diagnosed With Cancer by Site (N=10.1M)



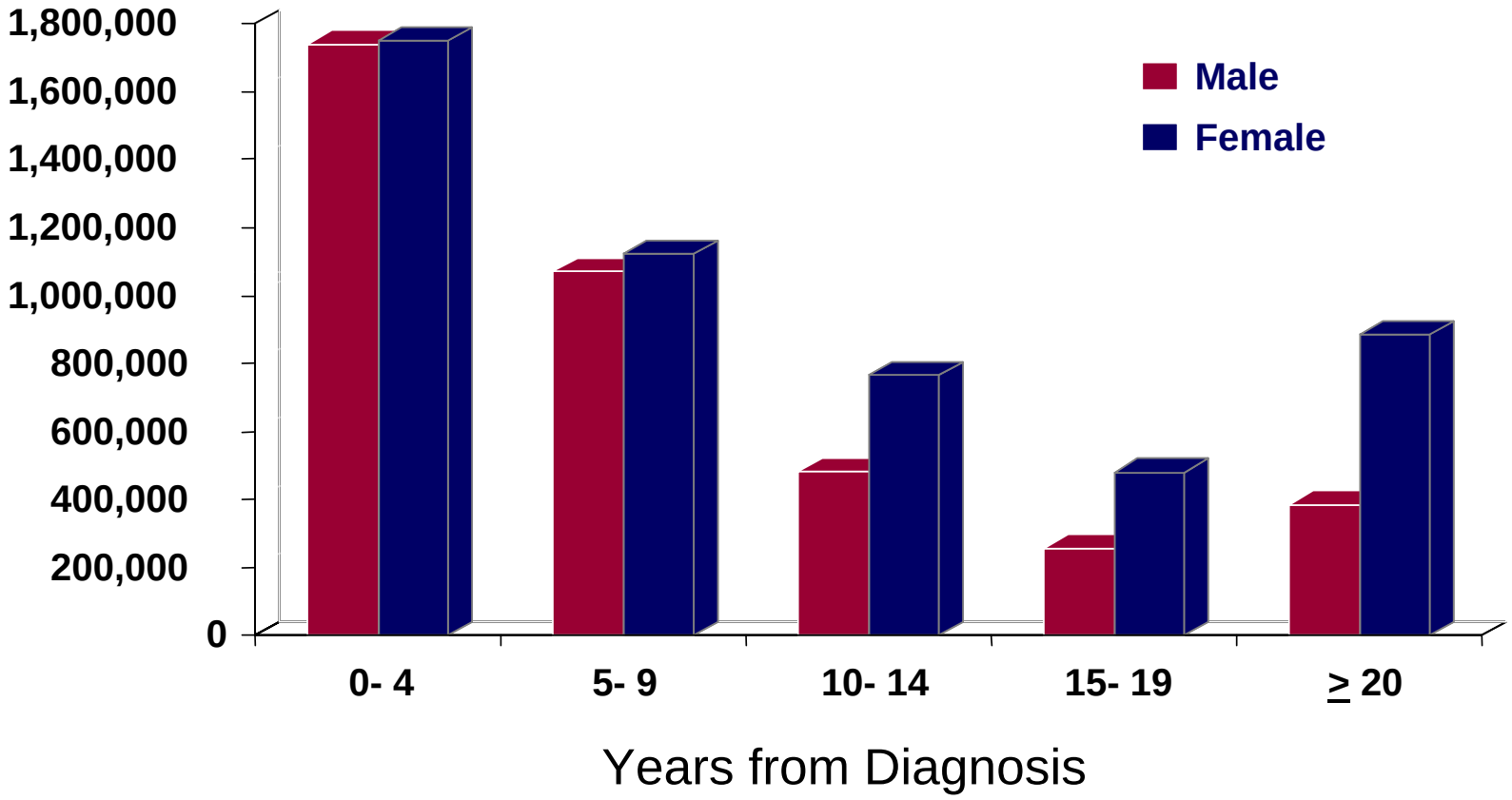
Source: NCI Office of Cancer Survivorship

Estimated Number of Cancer Survivors in the U.S. by Primary Site (N=10.1 Million)



Source: NCI Office of Cancer Survivorship

Estimated 10.1 Million Persons Alive in the U.S. Diagnosed with Cancer

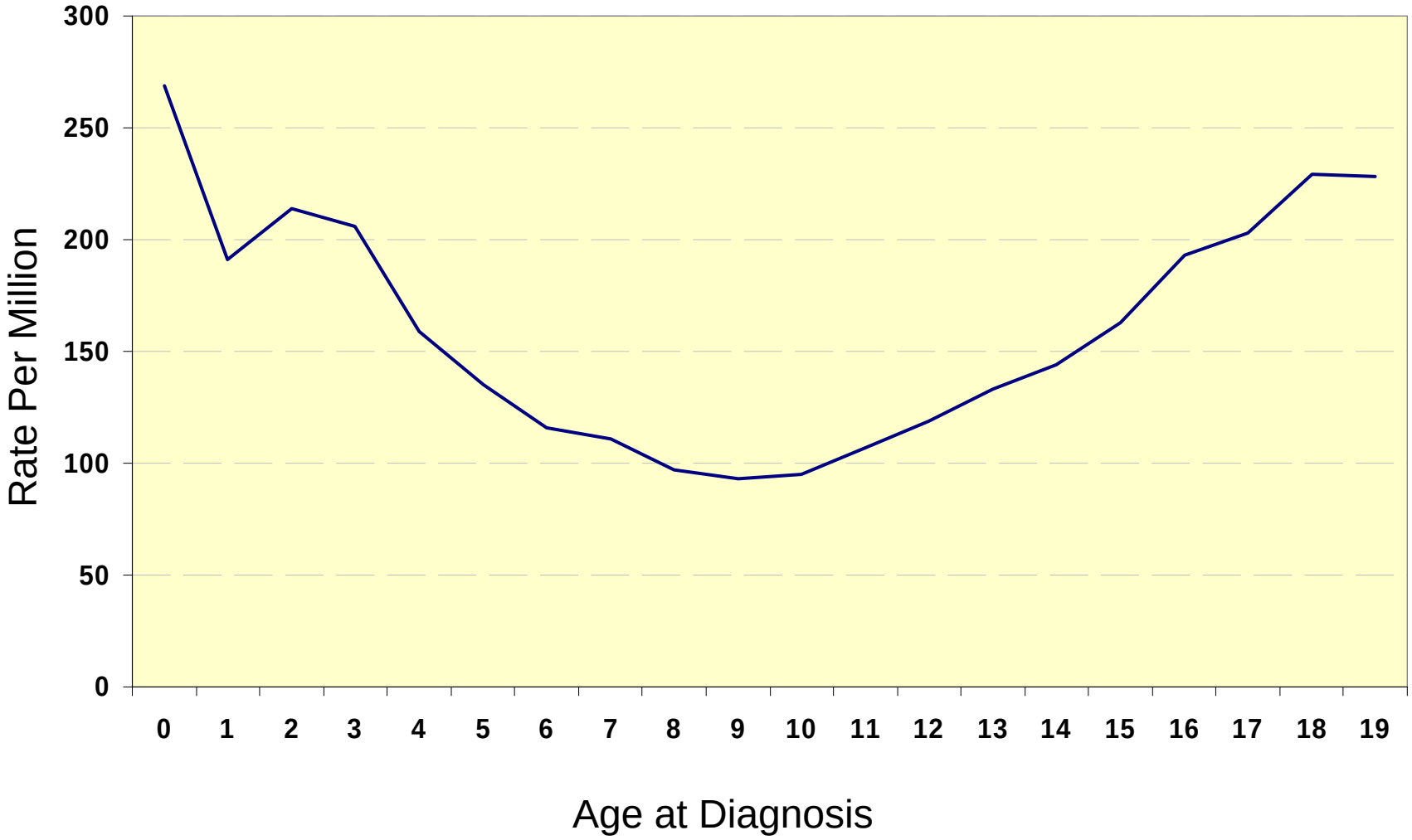


Source: SEER & NCI Office of Cancer Survivorship

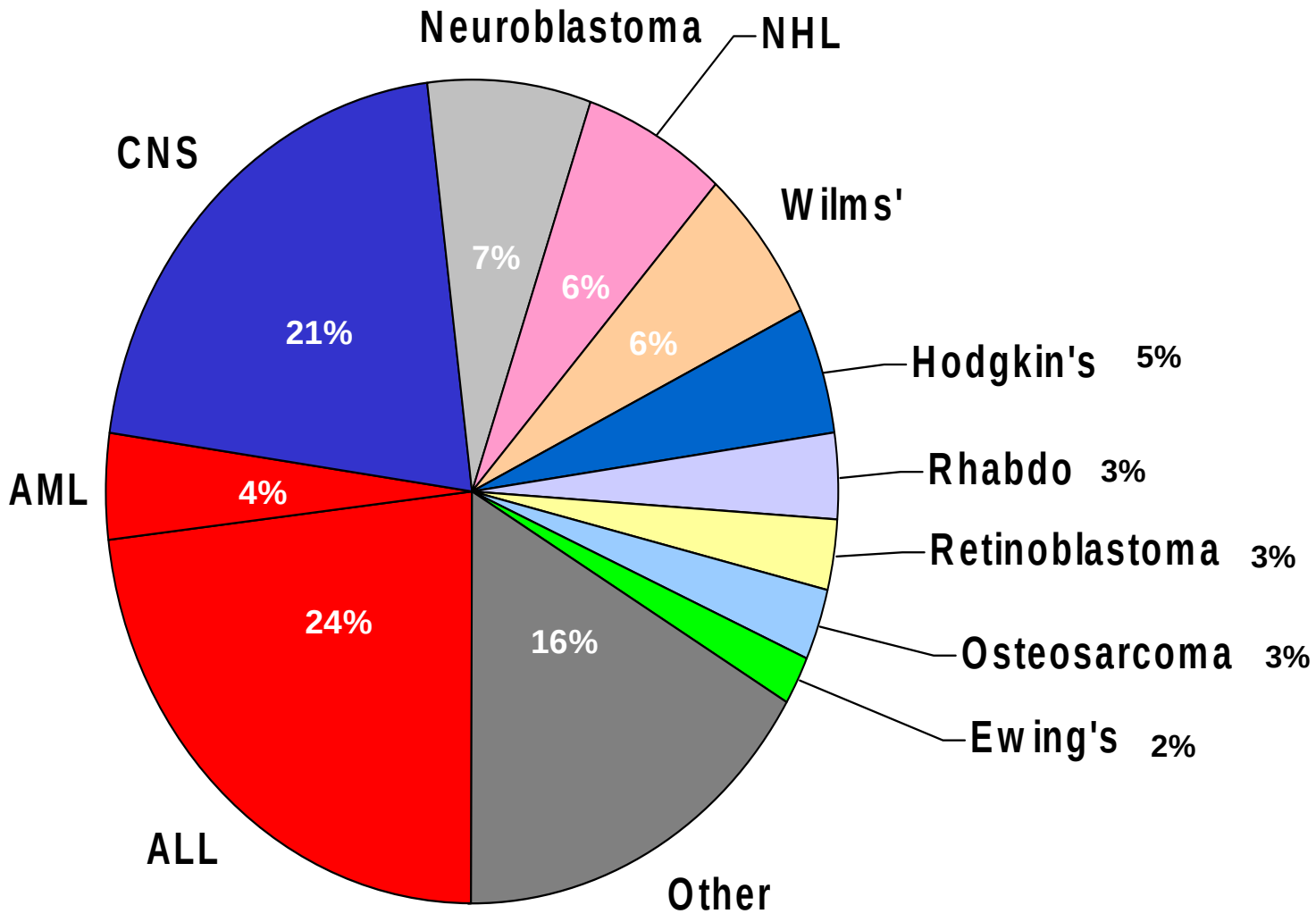
Age-Specific Incidence

ALL DIAGNOSES COMBINED

SEER Program 1986 - 2002

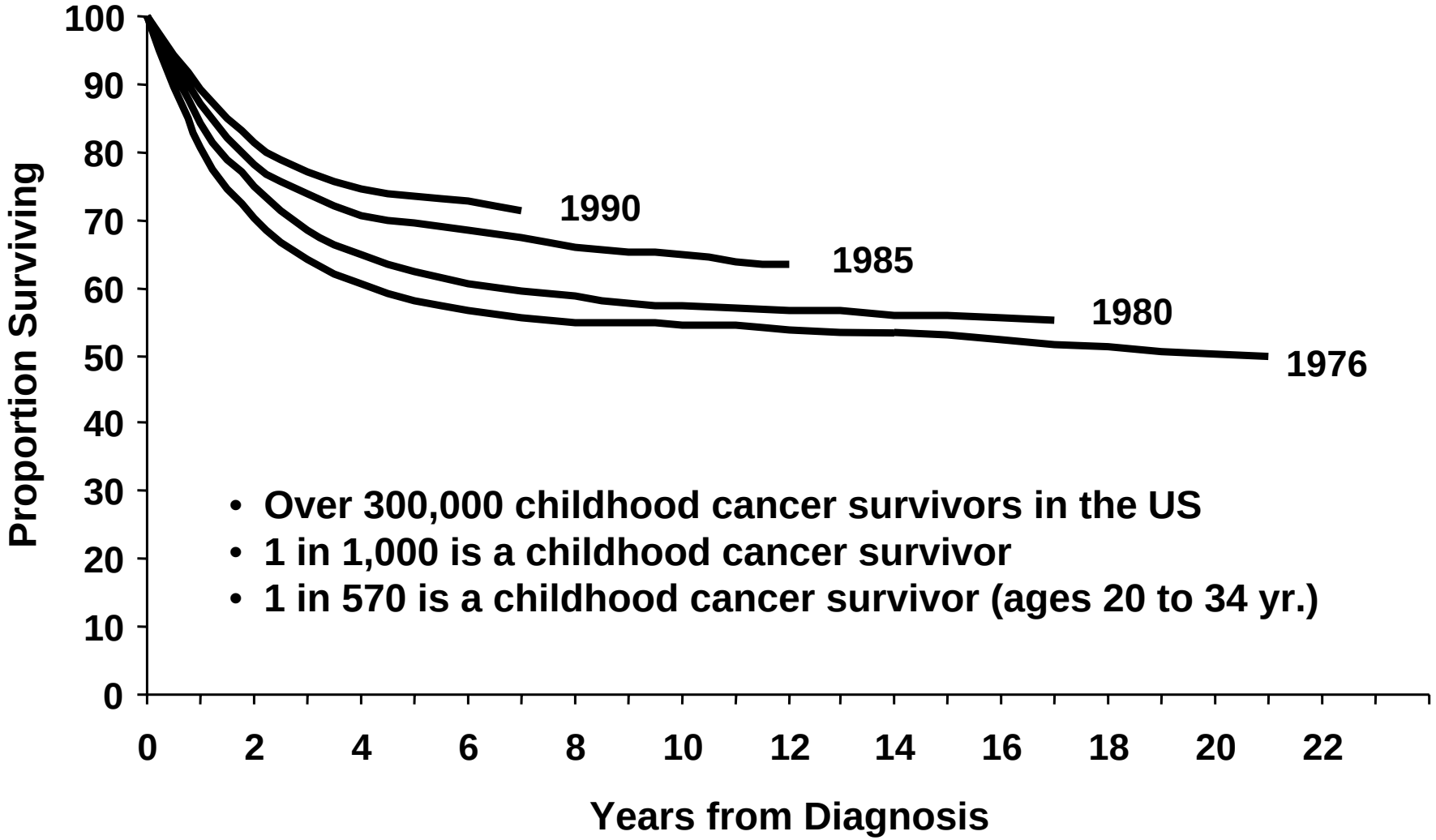


Distribution of Childhood Cancer in the U.S. (< 15 years) 1974-2002 SEER



Cancer Survival, 0-14 Years of Age

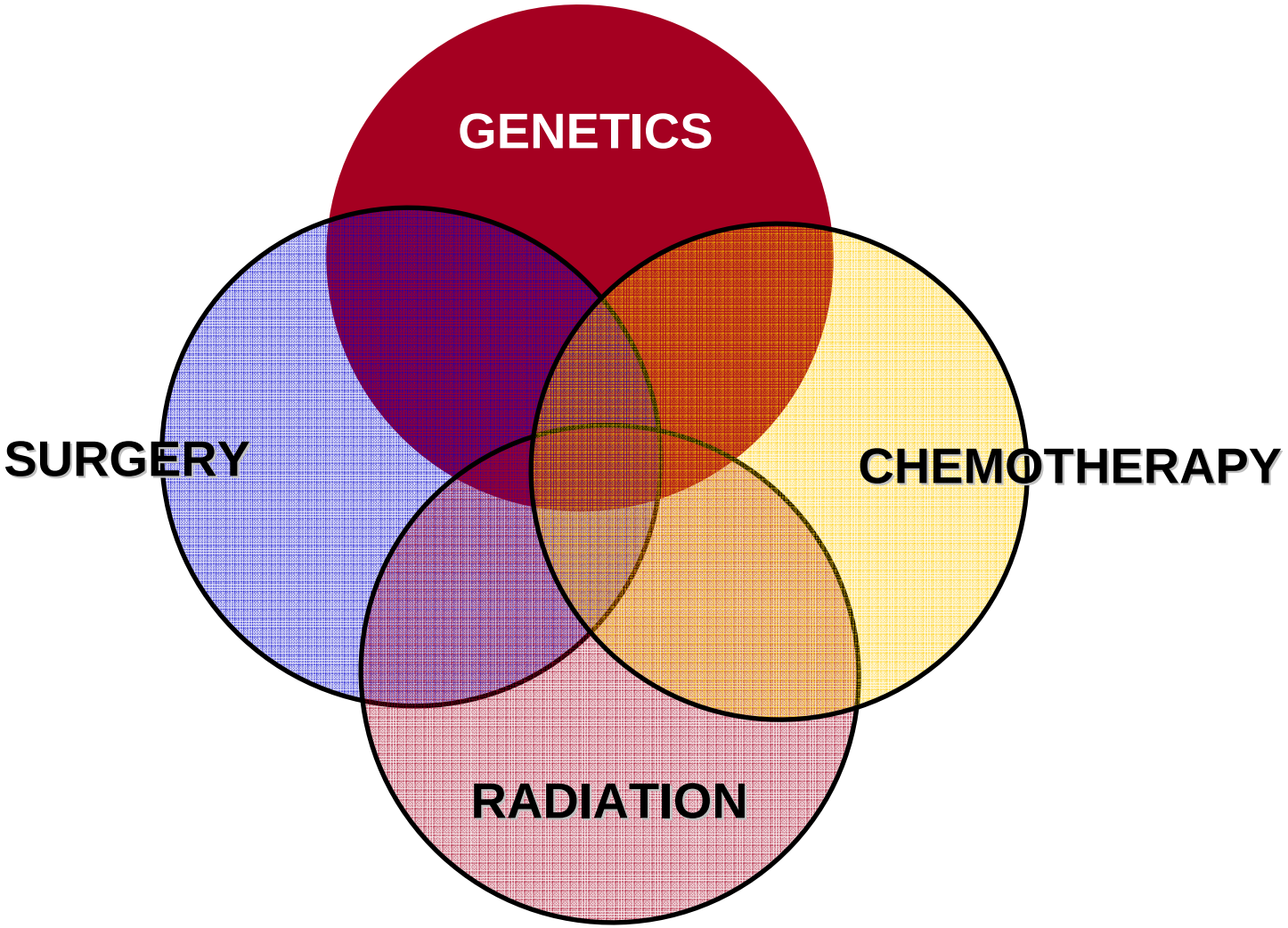
SEER Program 1976-1997



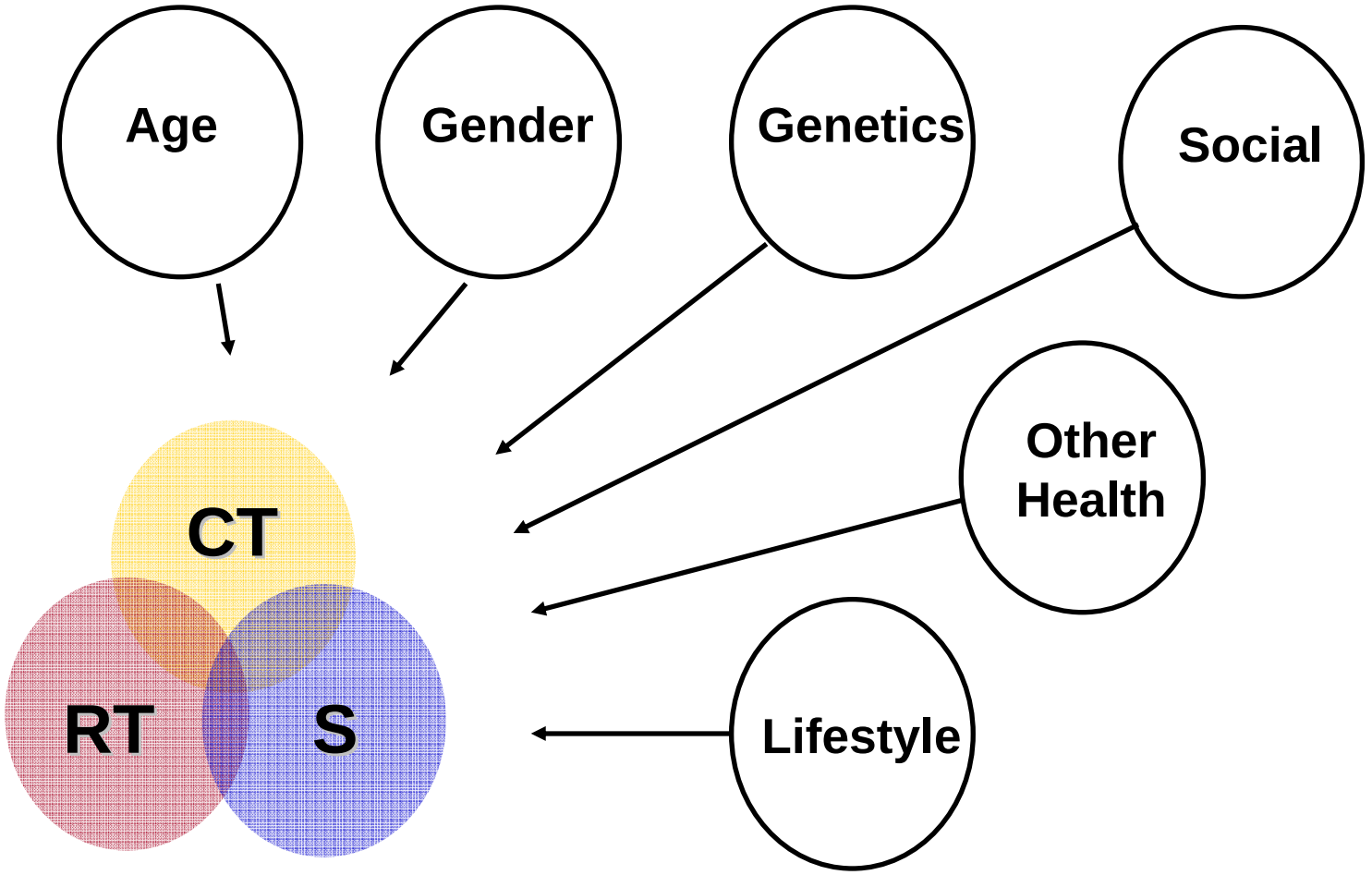
Selected Health-Related Outcomes of Childhood Cancer Survivors

- Cardiac/vascular
- Cytogenetic
- Dental
- Endocrinologic
- Educational
- Gastrointestinal
- Hearing
- Hepatic
- Neurologic
- Neuropsychologic
- Ophthalmologic
- Orthopedic
- Psychosocial
- Pulmonary
- Renal
- Reproduction
- Second Cancers
- Skeletal

Assessment of Risk for Late Effects



Factors to be Considered in Risk of Late Effects of Therapy



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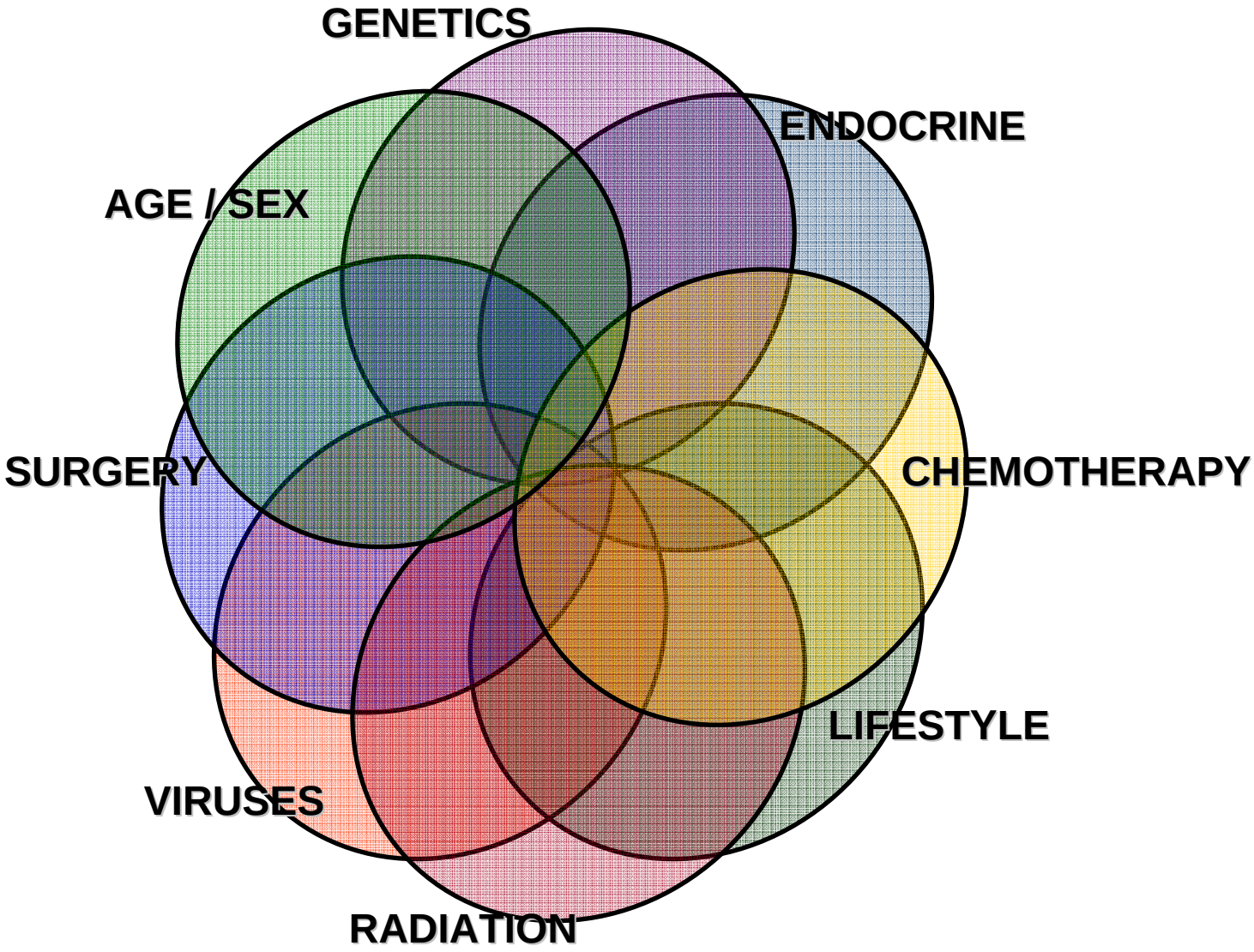


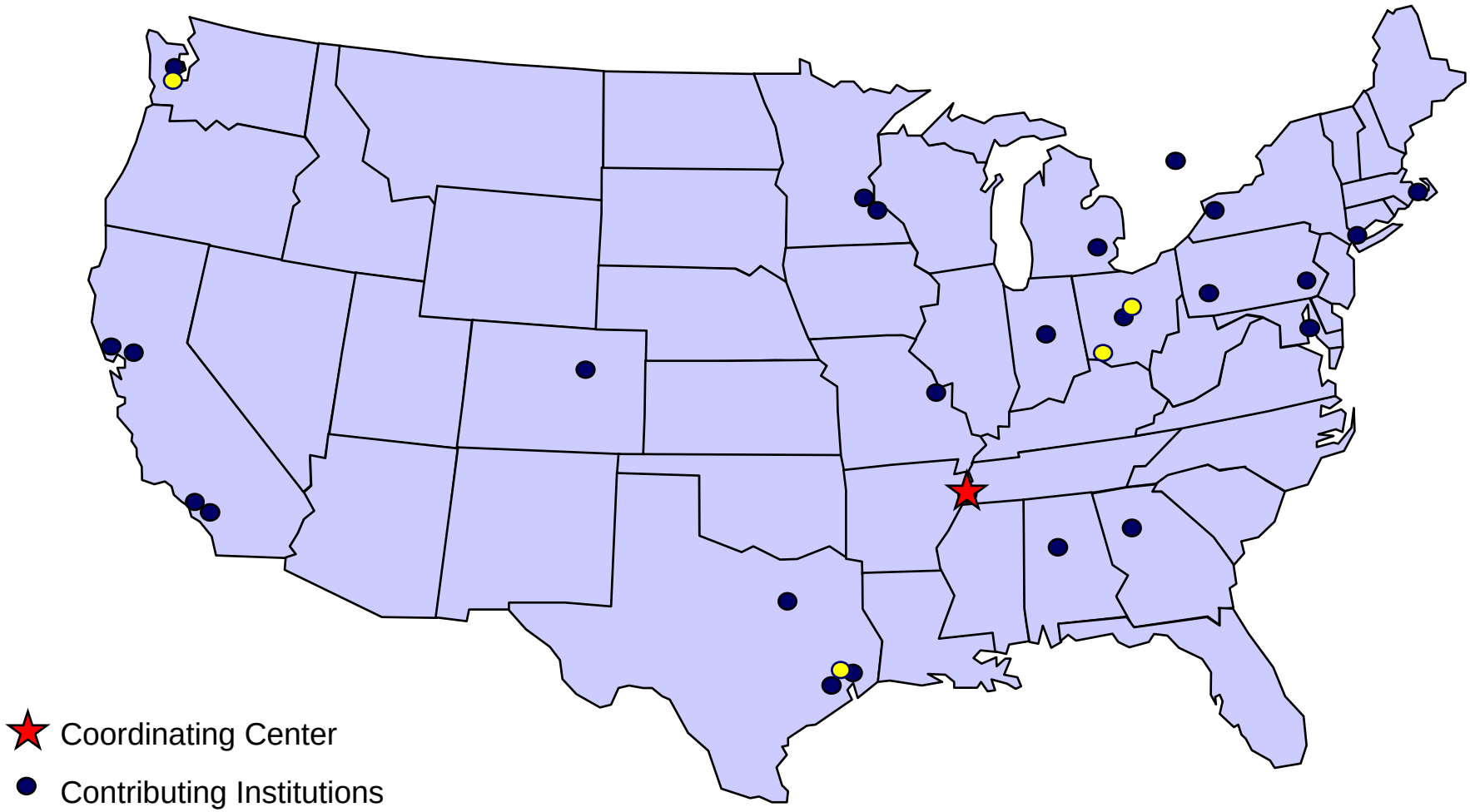
Participating Institutions

St. Jude Children's Research Hospital
University of Minnesota
Children's Hospital of Pittsburgh
Stanford University
Dana-Farber Cancer Institute
Children's National Medical Center
M.D. Anderson Cancer Center
Memorial Sloan-Kettering Cancer Center
Texas Children's Hospital
University of California, San Francisco
Seattle Children's Hospital
Toronto Hospital for Sick Children
Denver Children's Hospital
Children's Hospital of Columbus
Emory University

Roswell Park Cancer Center
Mayo Clinic
Children's Health Care Minneapolis
Children's Hospital of Philadelphia
St. Louis Children's Hospital
Children's Hospital of Los Angeles
UCLA Medical Center
Miller Children's Hospital Long Beach
Children's Hospital of Orange County
Riley Hospital for Children – Indiana Univ.
UAB/Children's Hospital of Alabama
University of Michigan – Mott Children's
Children's Medical Center of Dallas
Fred Hutchinson Cancer Research Center

Childhood Cancer Survivor Study

Participating Institutions

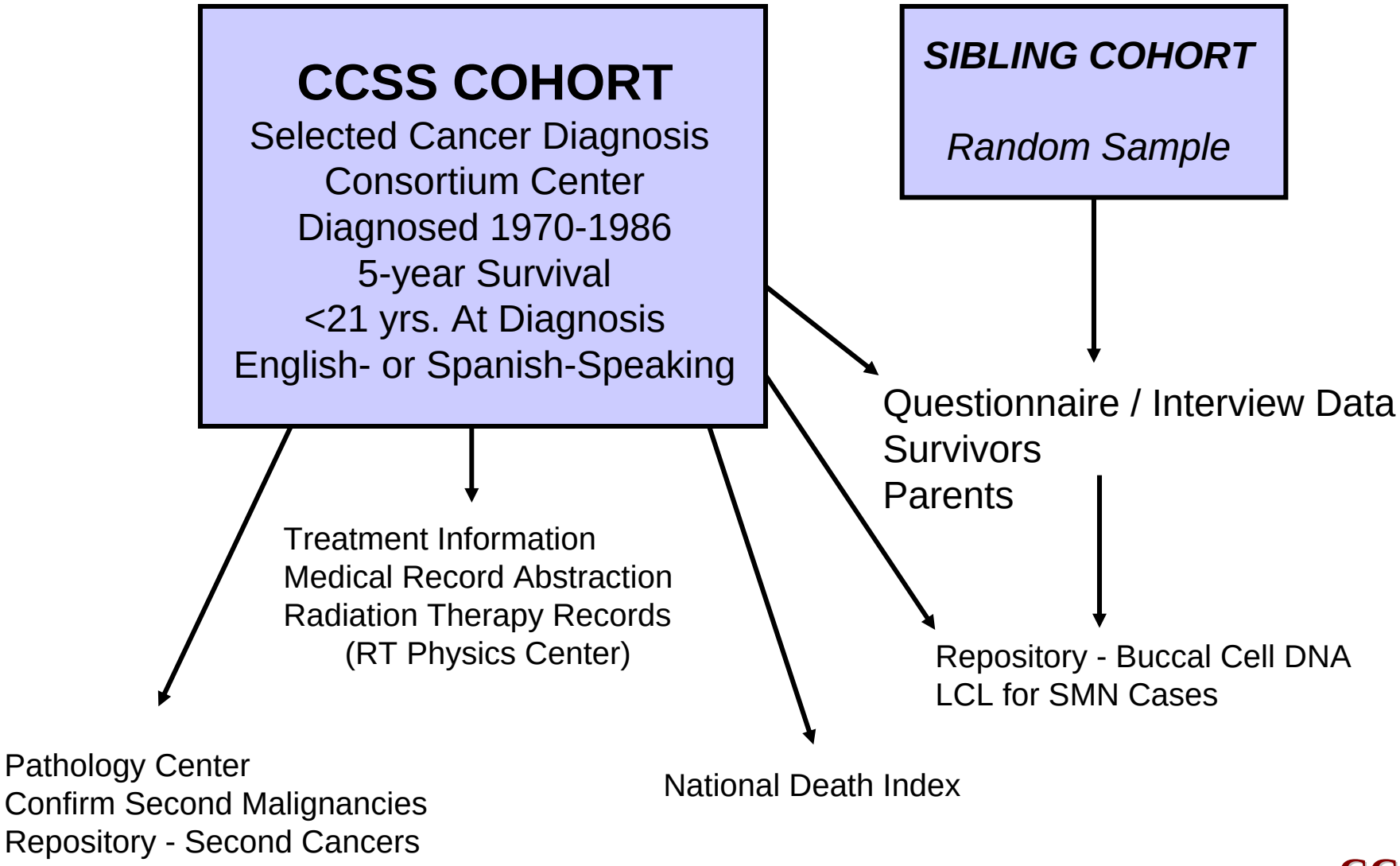


Coordinating Center

Contributing Institutions

Resource Center

Study Overview



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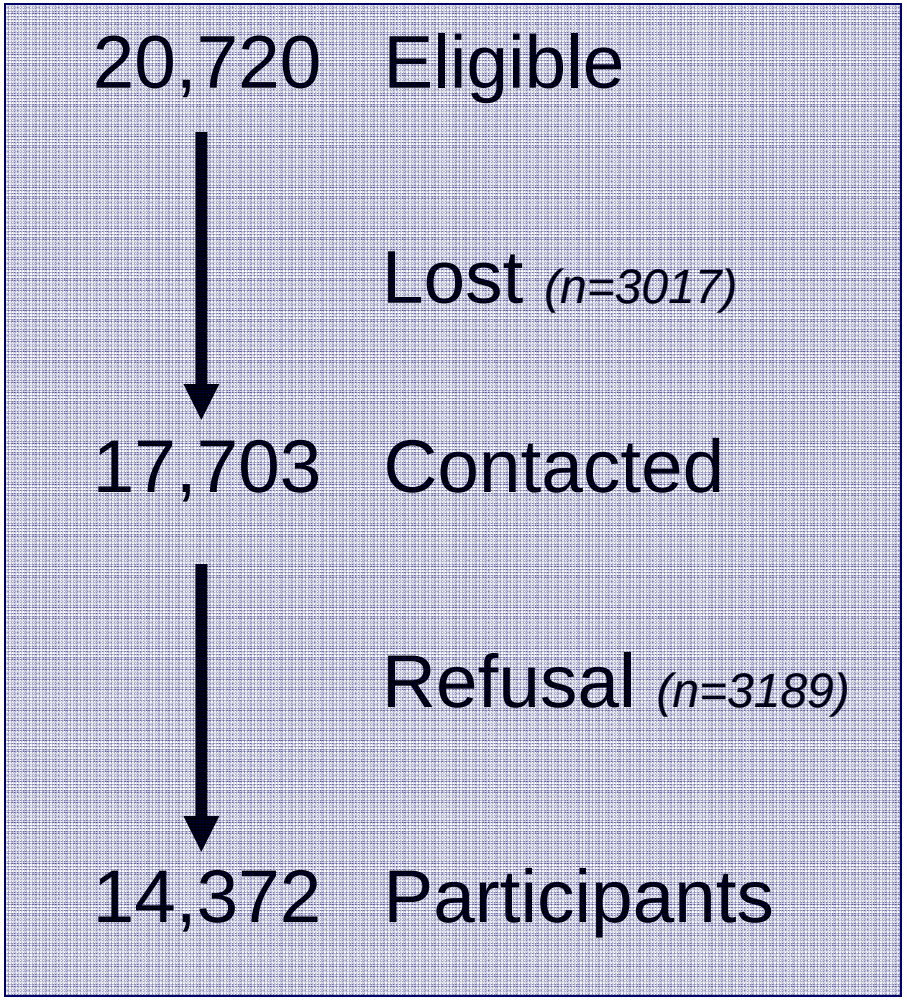
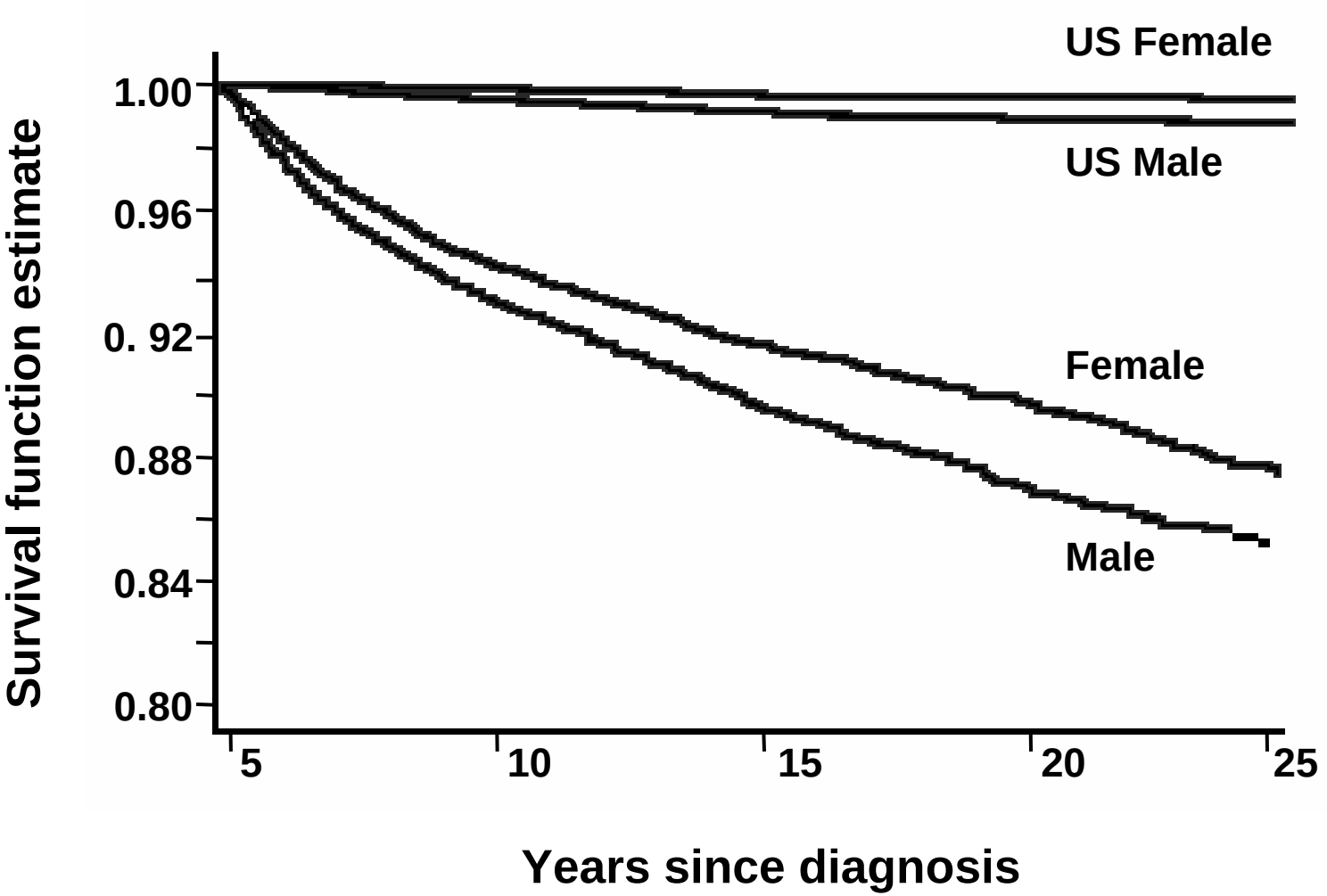


Late Morality Among 5+ Year Survivors

Late Mortality in 5+ Year Survivors

All Cause Mortality



Mertens et al, JCO, 2000

Late Mortality in 5+ Year Survivors

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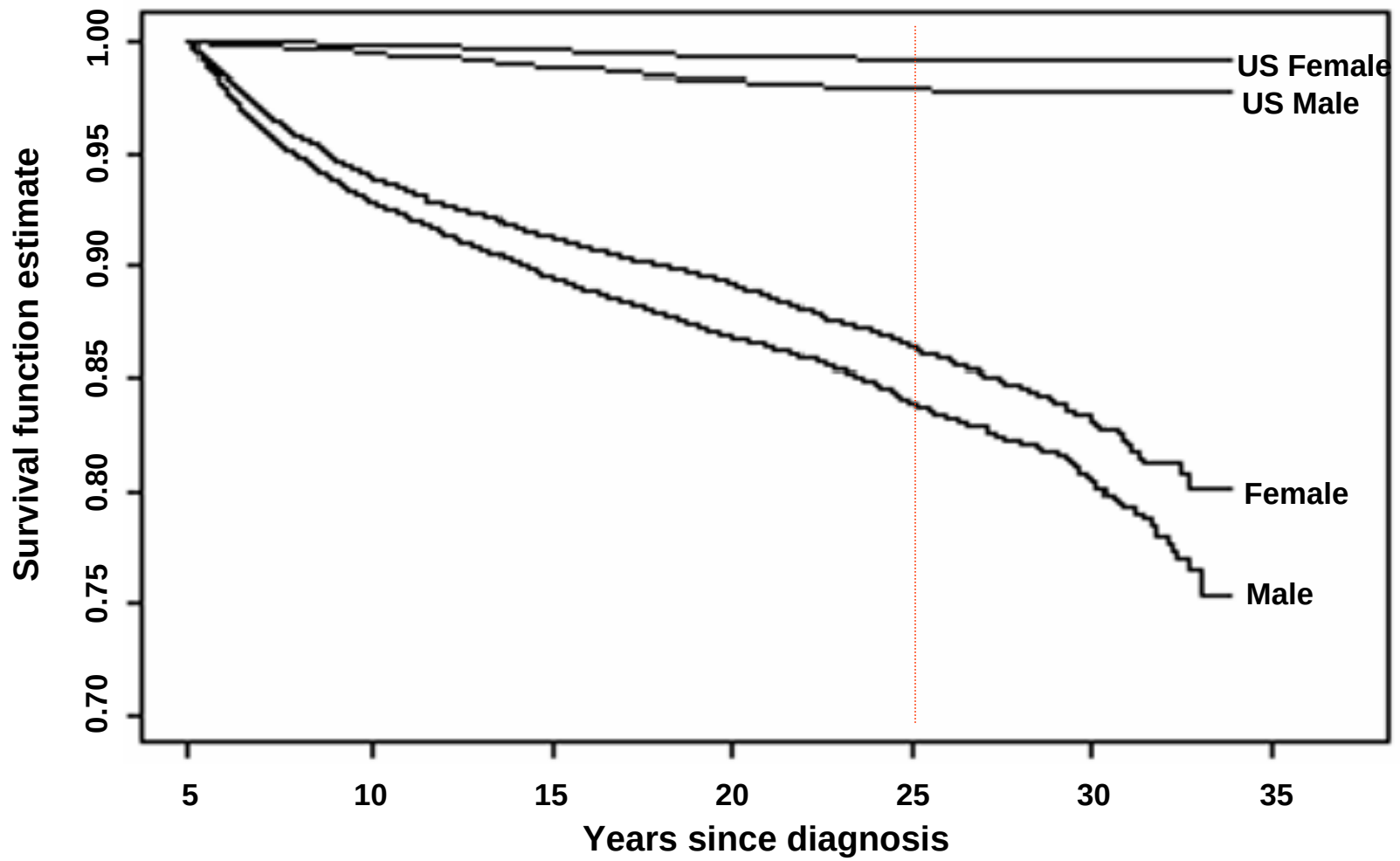


Mertens, et al, ASCO, 2005

Late Mortality in 5+ Year Survivors

Causes of Death

Recurrence	1264	65%
Treatment-Related	404	22%
Other Causes	221	13%

Late Mortality in 5+ Year Survivors

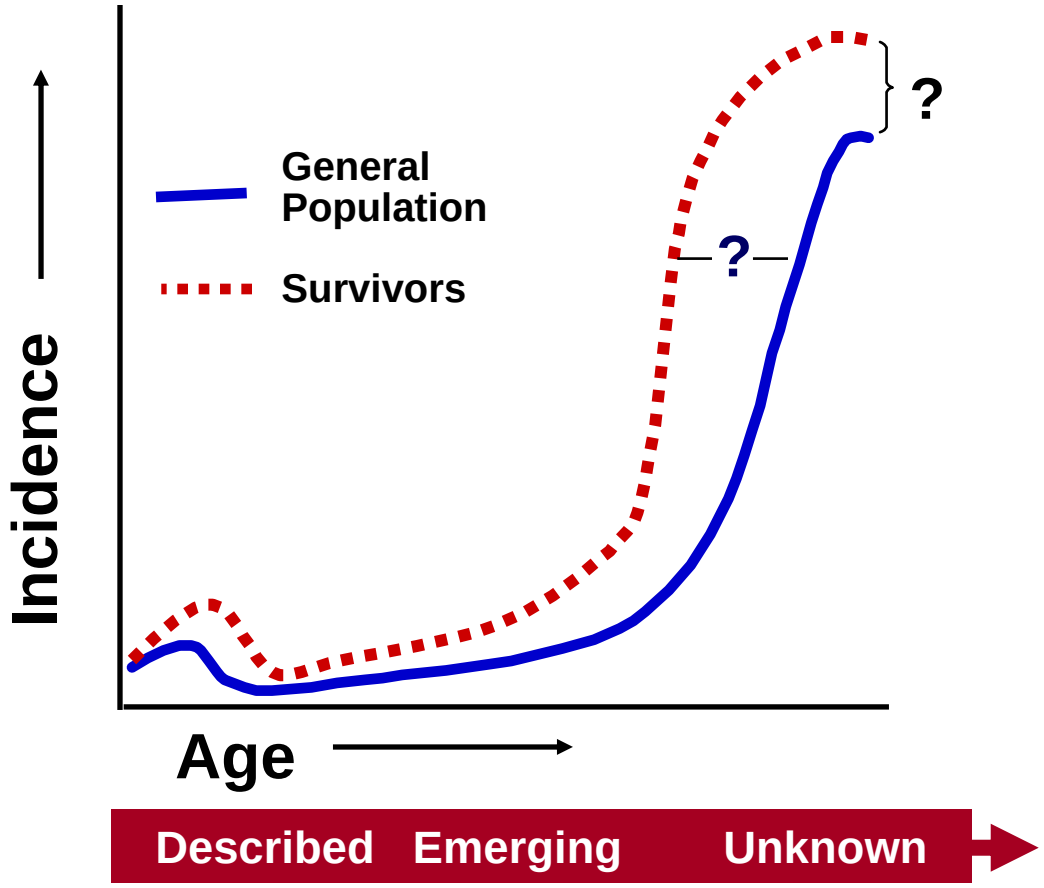
Treatment-related Mortality

	# deaths	SMR	(95% CI)
Cancer	243	16.59	(14.6 -18.8)
Cardiac	84	10.40	(8.3 -12.8)
Pulmonary	33	8.23	(5.7 -11.4)

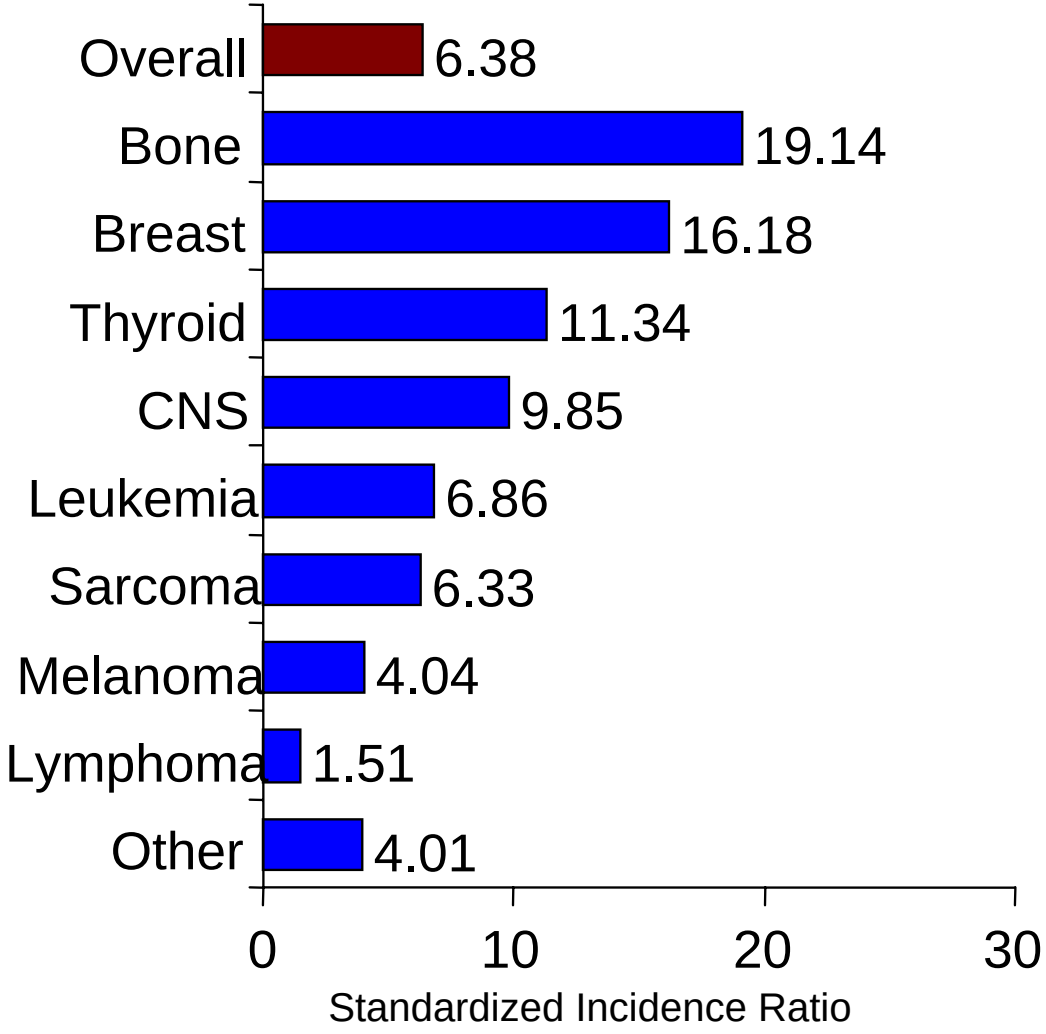
Subsequent Neoplasms

How Might Cancer-Related Factors Impact Subsequent Health?

SECOND MALIGNANCIES AS A MODEL

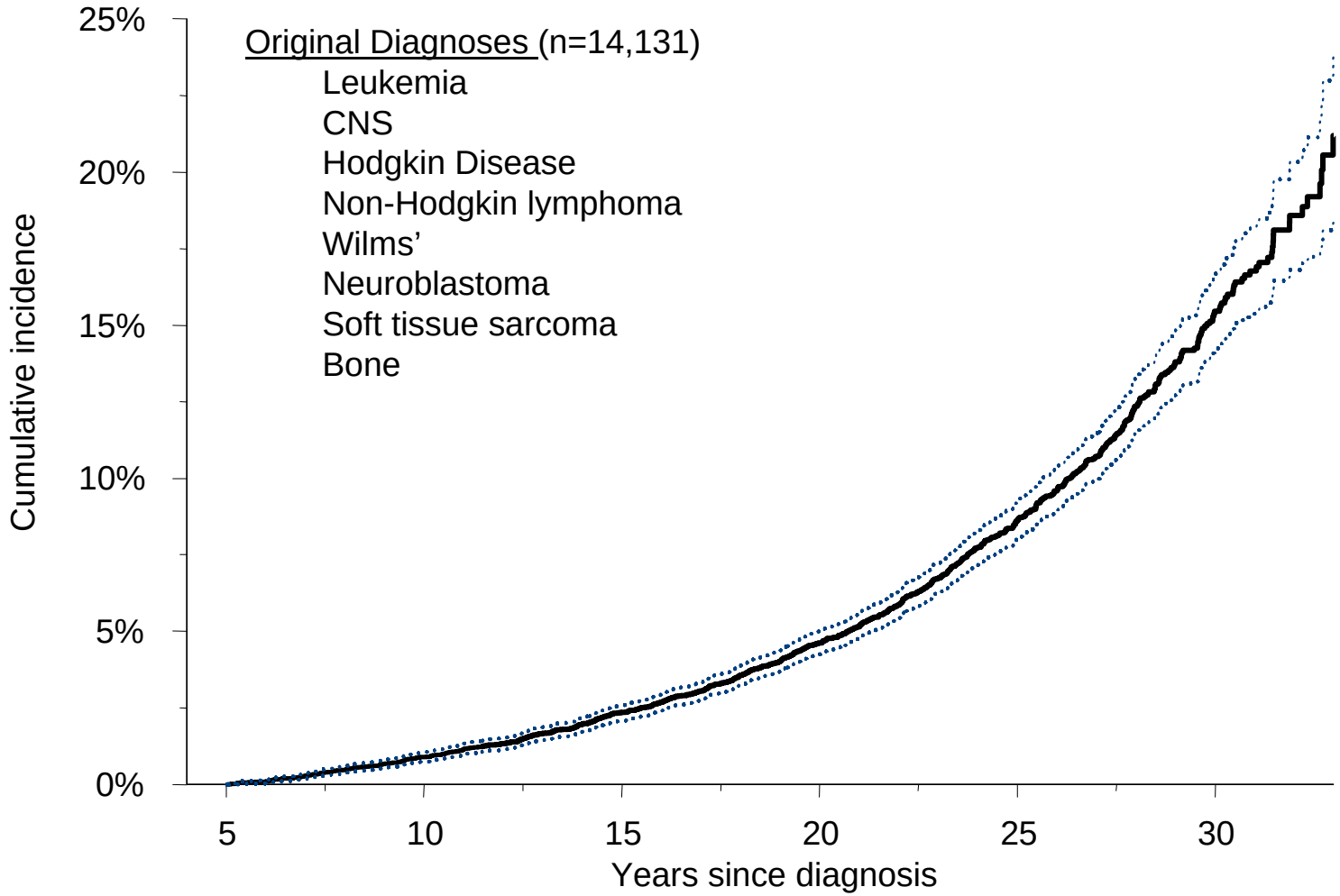


Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer



Neglia et al, JNCI 2001

Malignancies Occurring 5+ years (n=1039)
Including Nonmelanoma Skin Cancer



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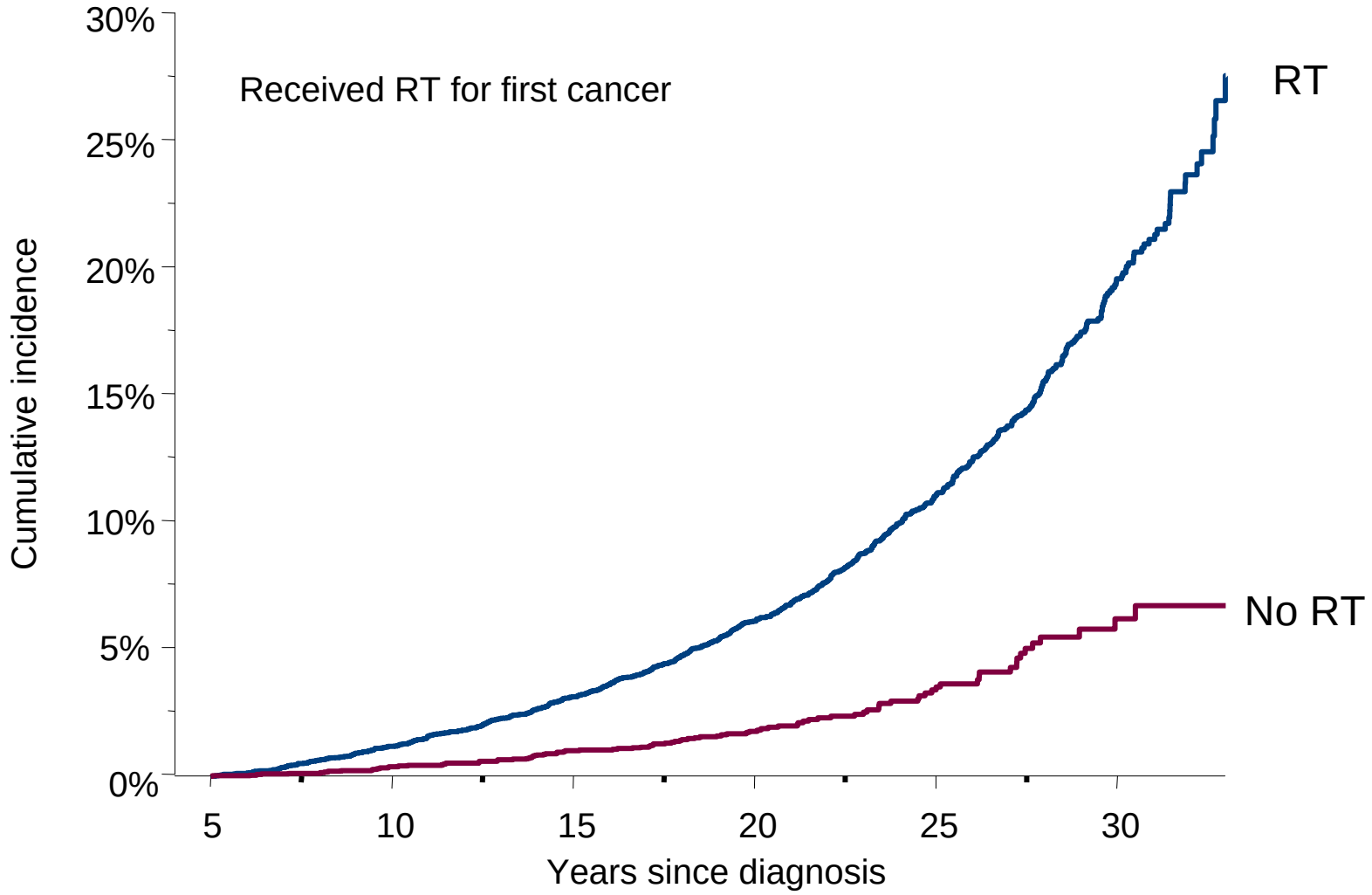

Malignancies Occurring 5+ years
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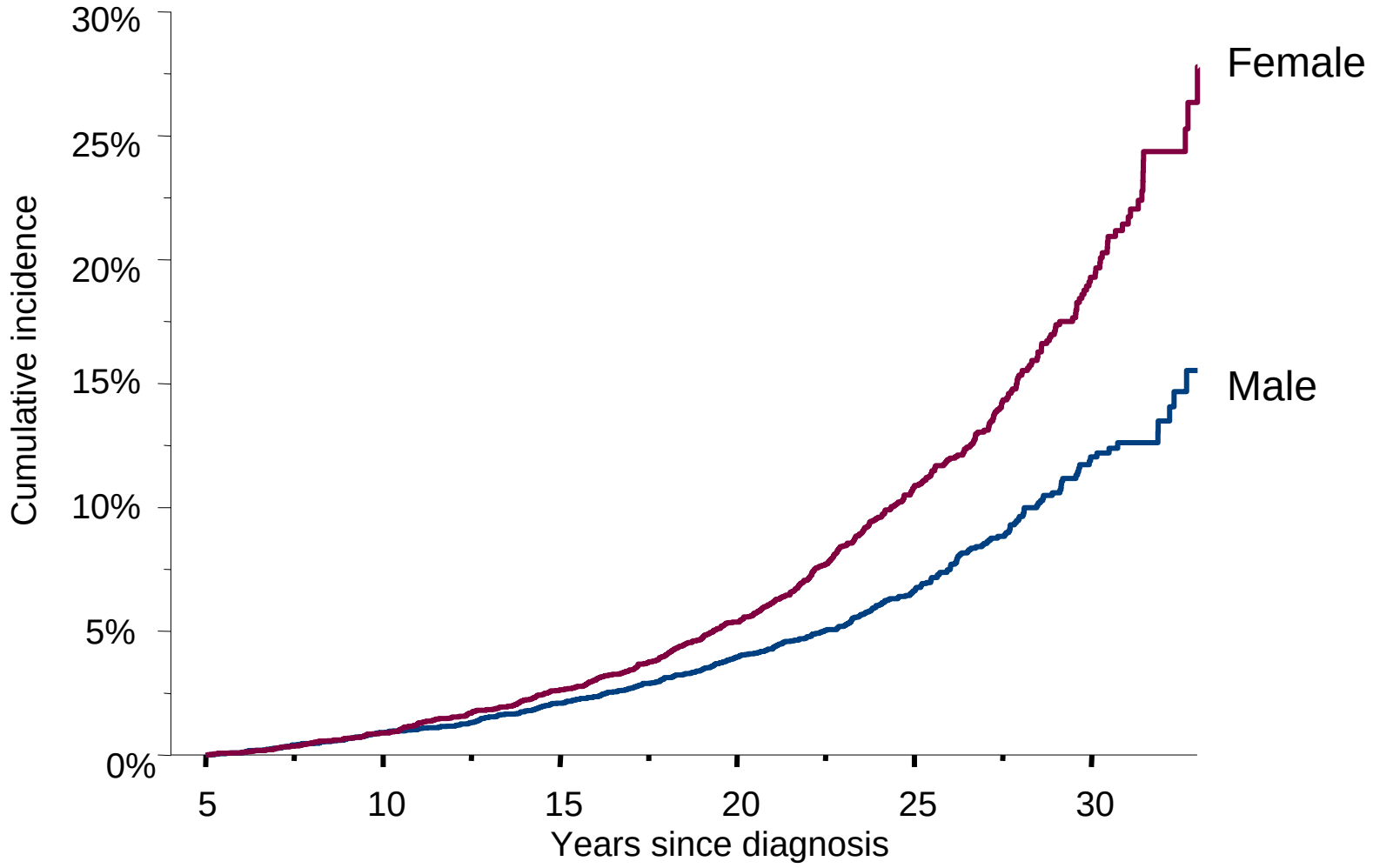
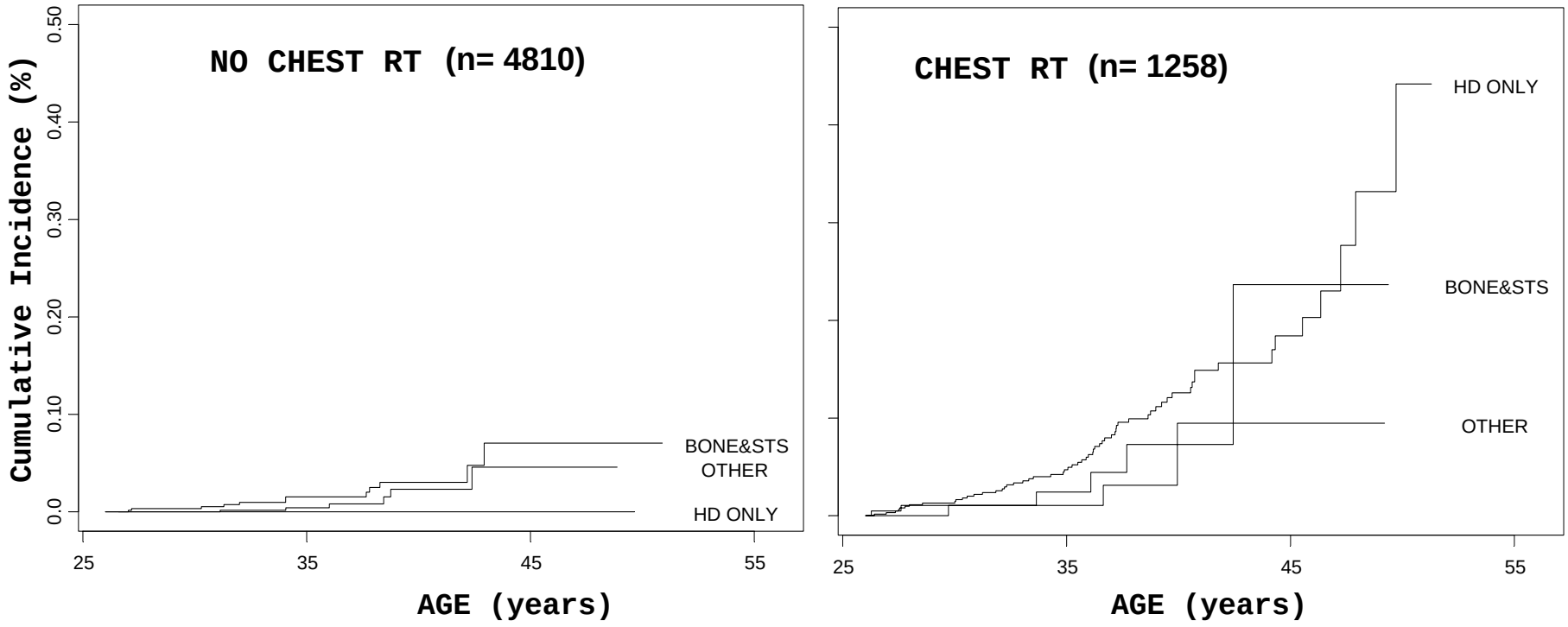


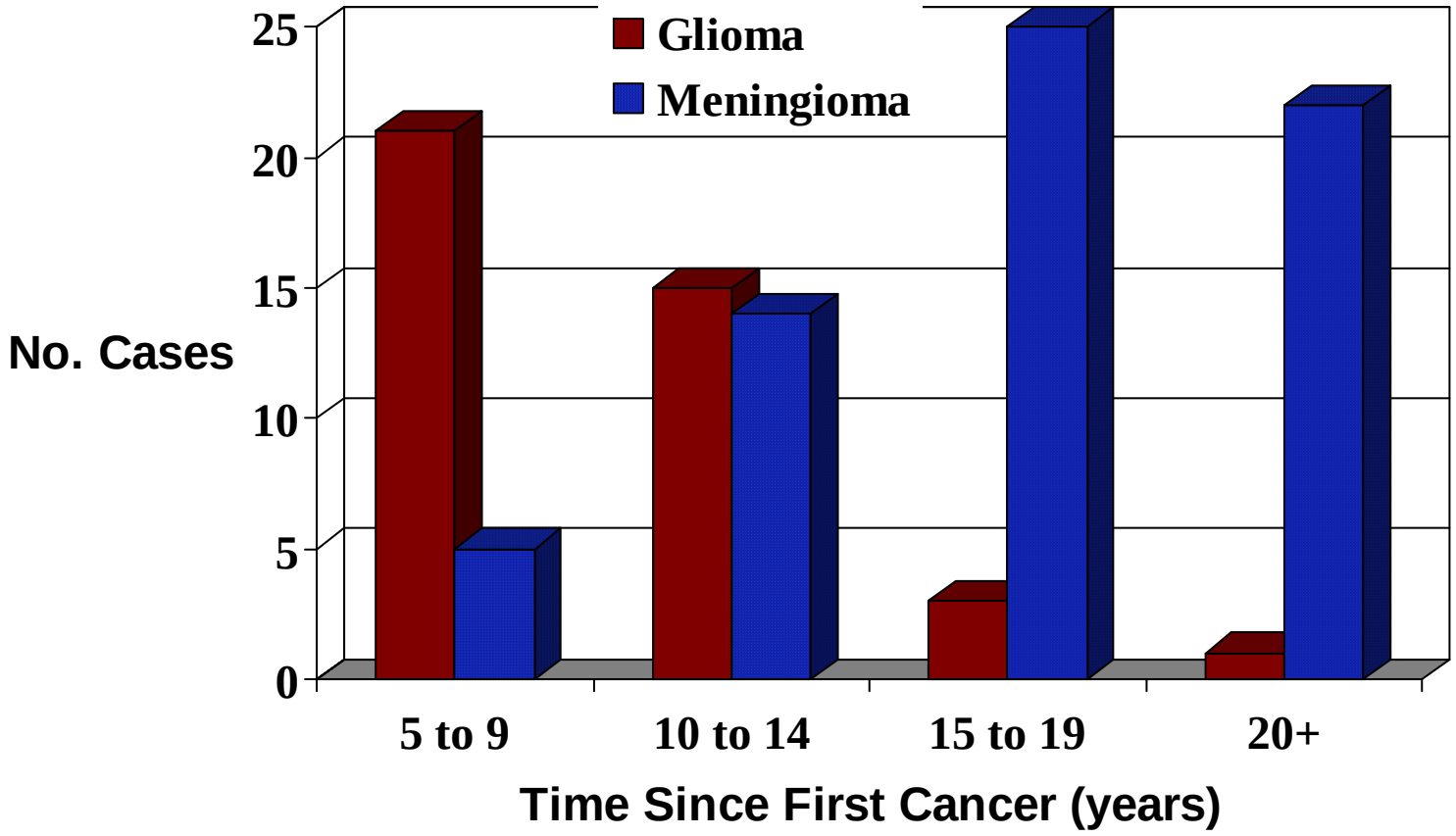
Breast Cancer
in Adult Female Survivors of Childhood Cancer

Cumulative Incidence



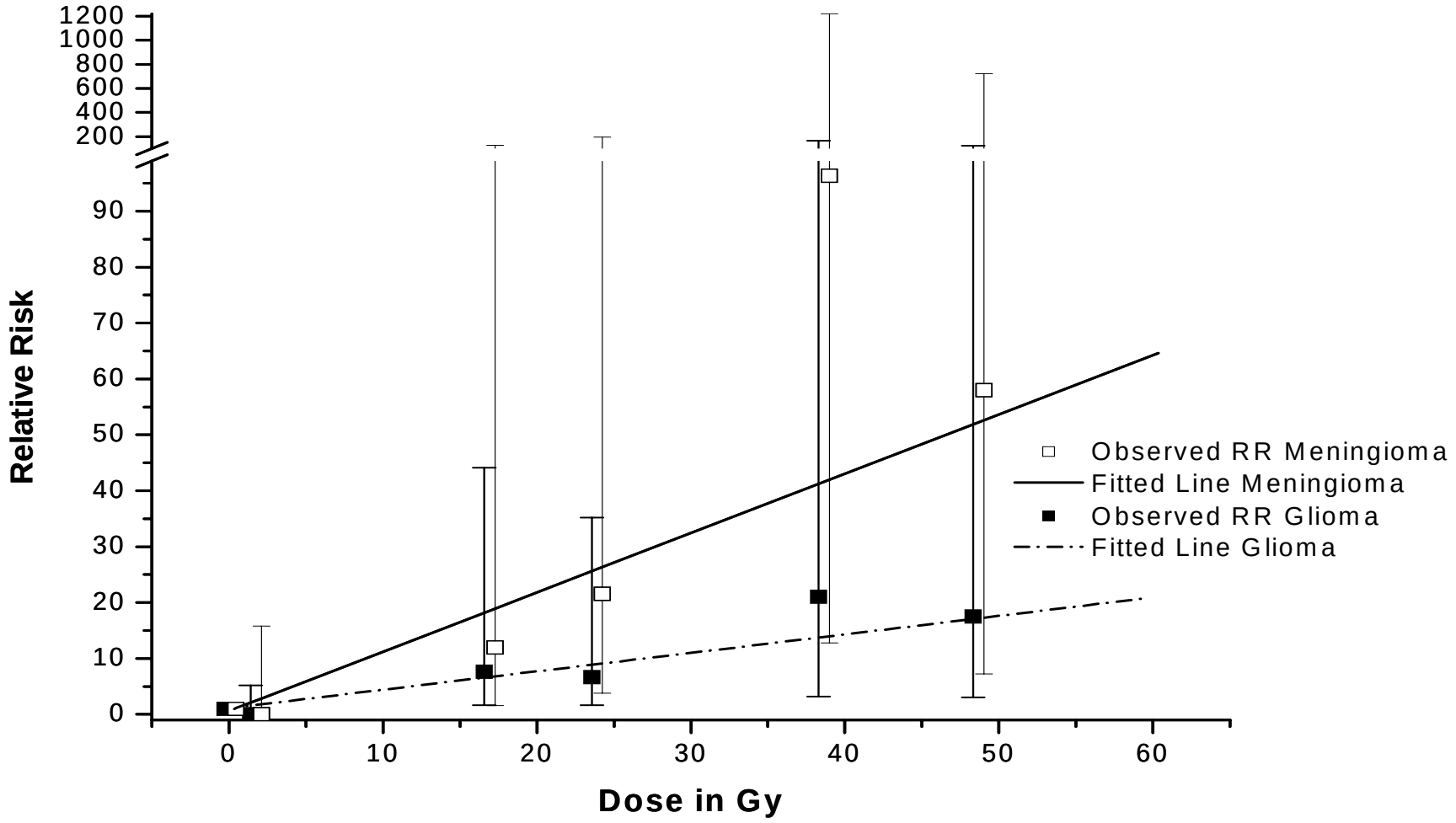
Kinney et al. Ann Intern Med 2004: 141:590-97

Brain Tumors Following Childhood Cancer
Glioma vs. Meningioma



J. Neglia and P. Inskip, In Press

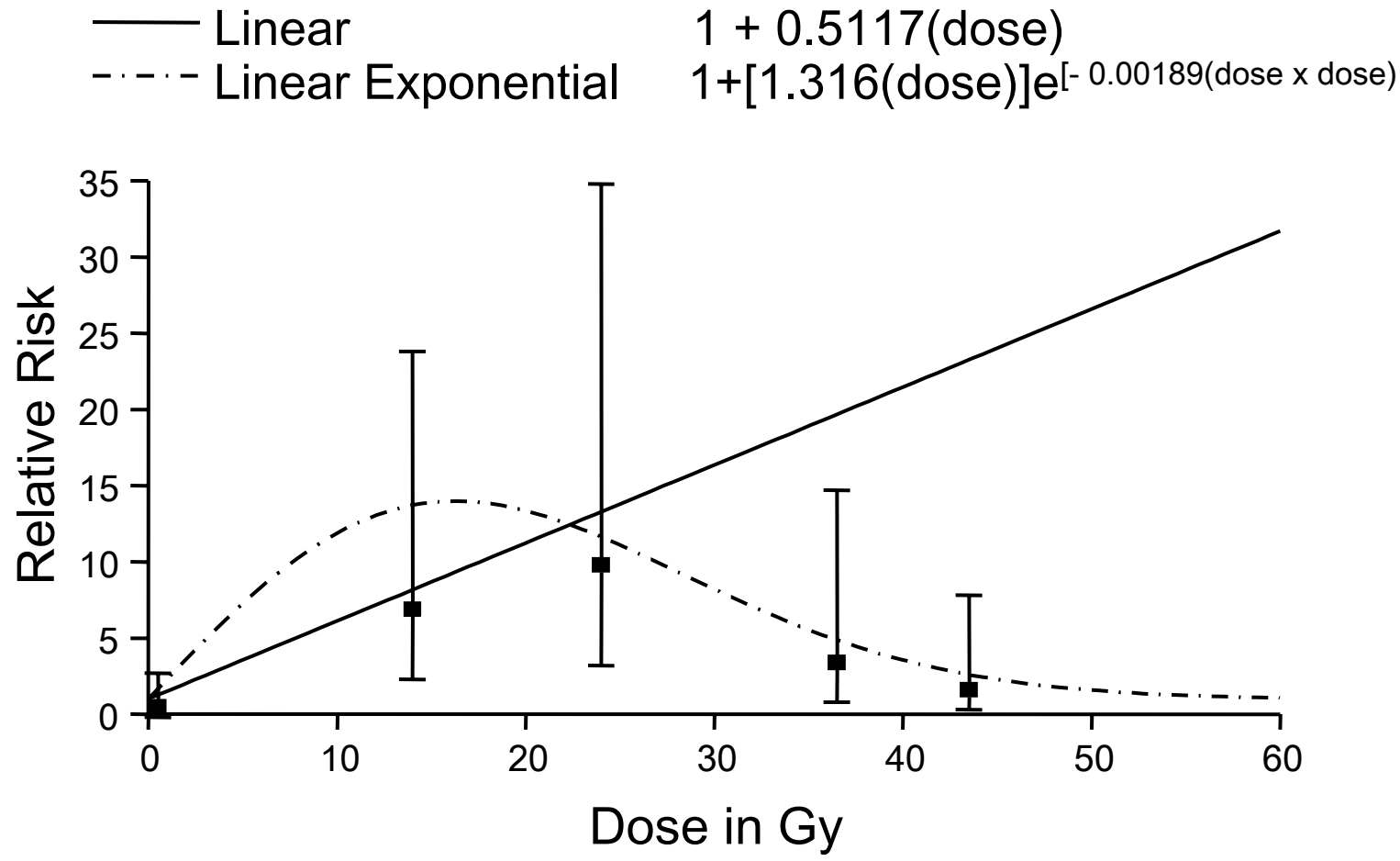
Brain Tumors Following Childhood Cancer
Risk by Radiation Dose



J. Neglia and P. Inskip, In Press

Thyroid Malignancy Among Long-term Survivors of Childhood Cancer

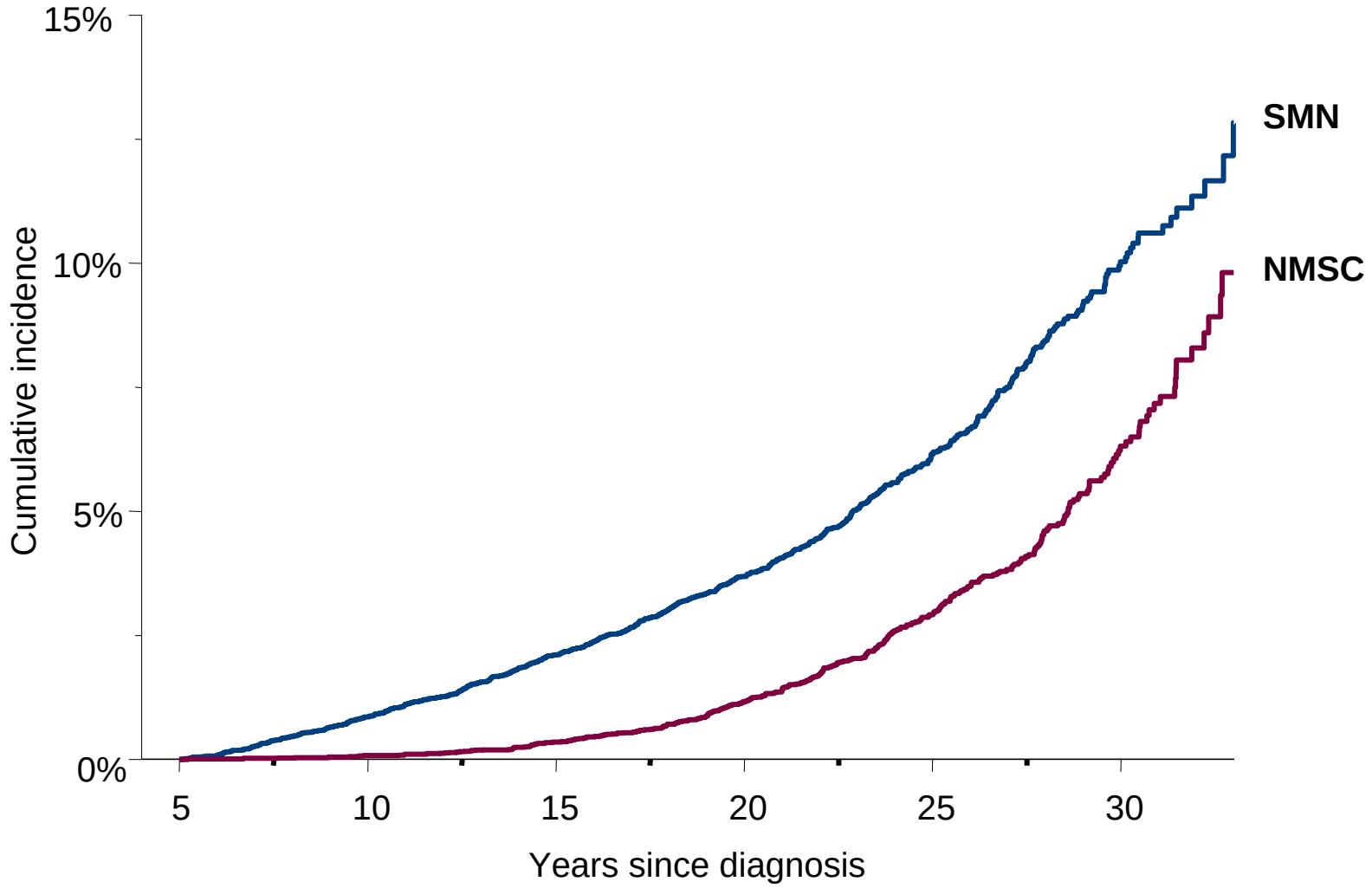
Dose Response Models of Relative Risk



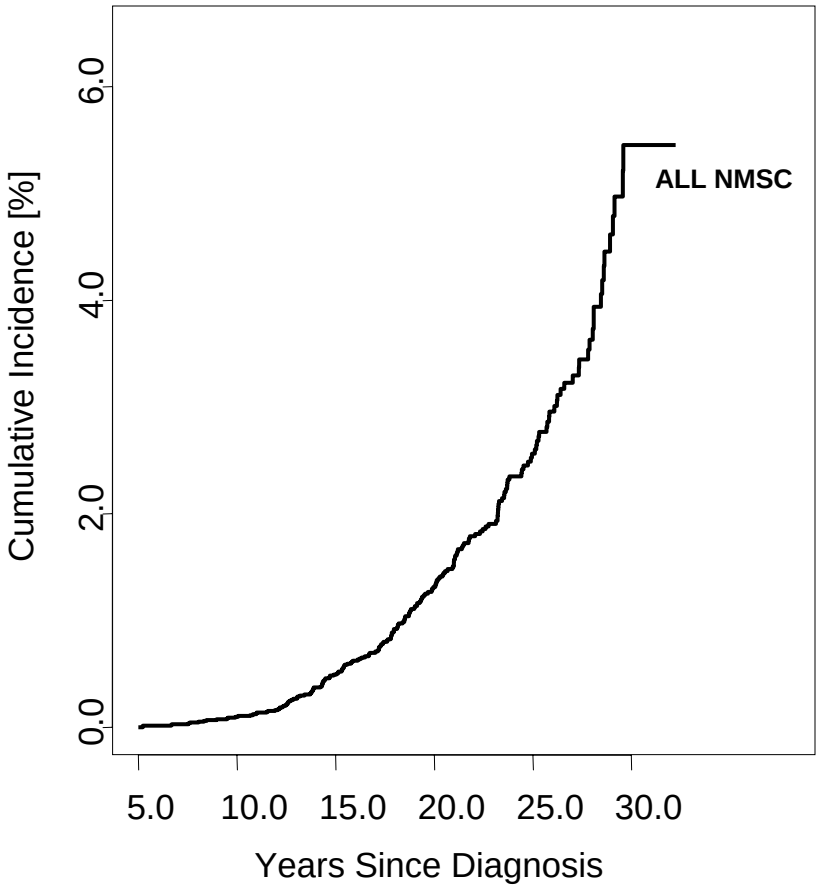
Sigurdson et al, Lancet, 2005

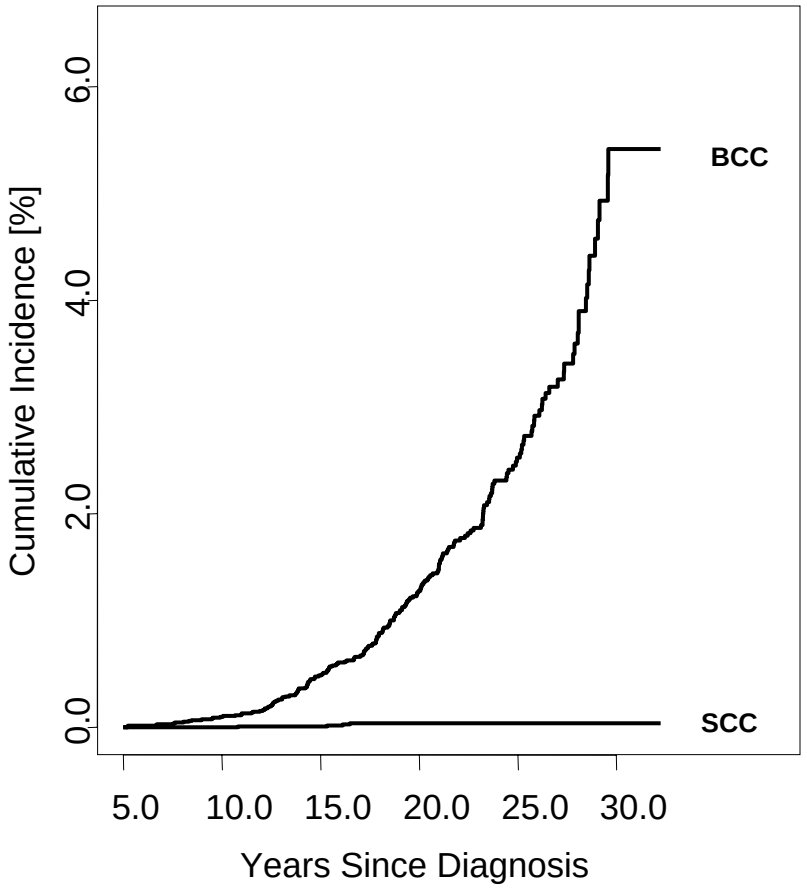
Malignancies Occurring 5+ years

Categorization of Cancer: SMN (Excludes NMSC)



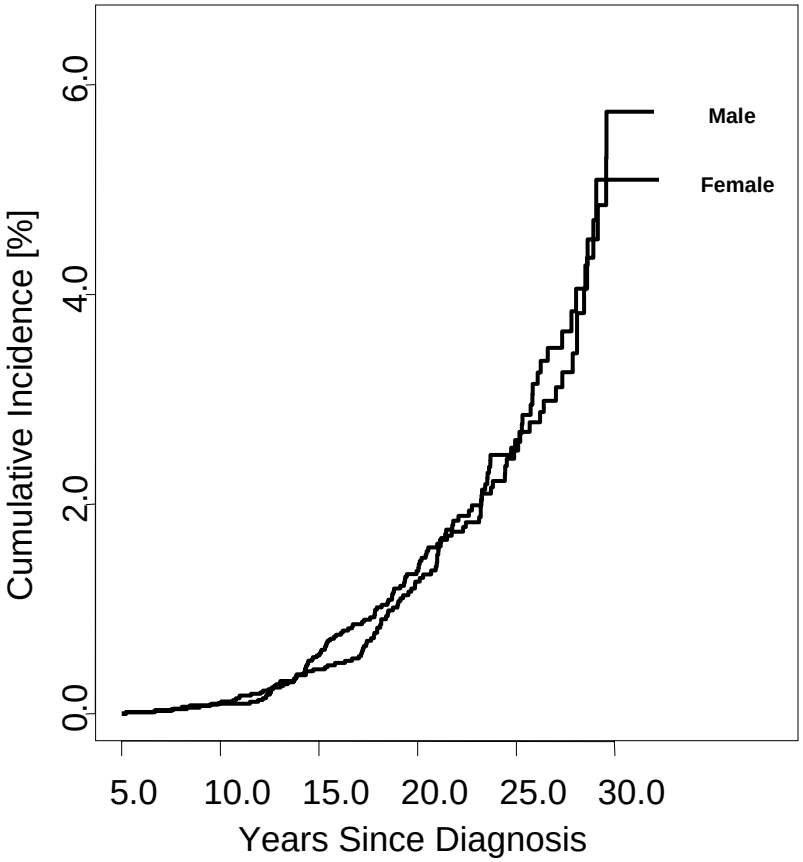
Nonmelanoma Skin Cancer Among Survivors of Childhood Cancer
Basal Cell vs. Squamous Cell

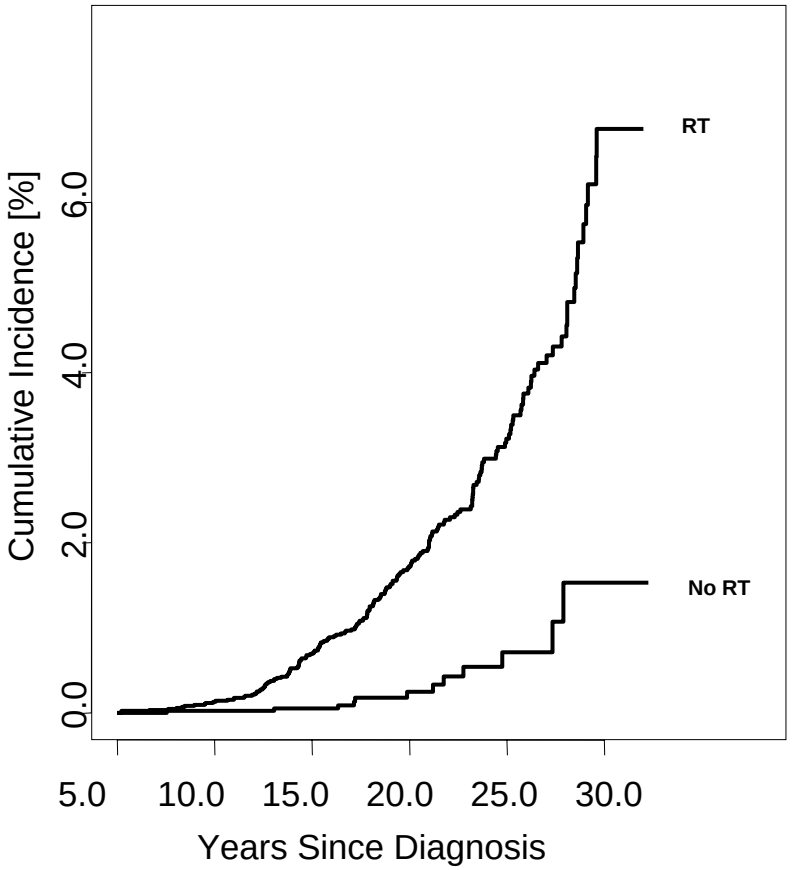




Perkins , et al., JCO 2005

Nonmelanoma Skin Cancer Among Survivors of Childhood Cancer
Gender and Radiation Therapy

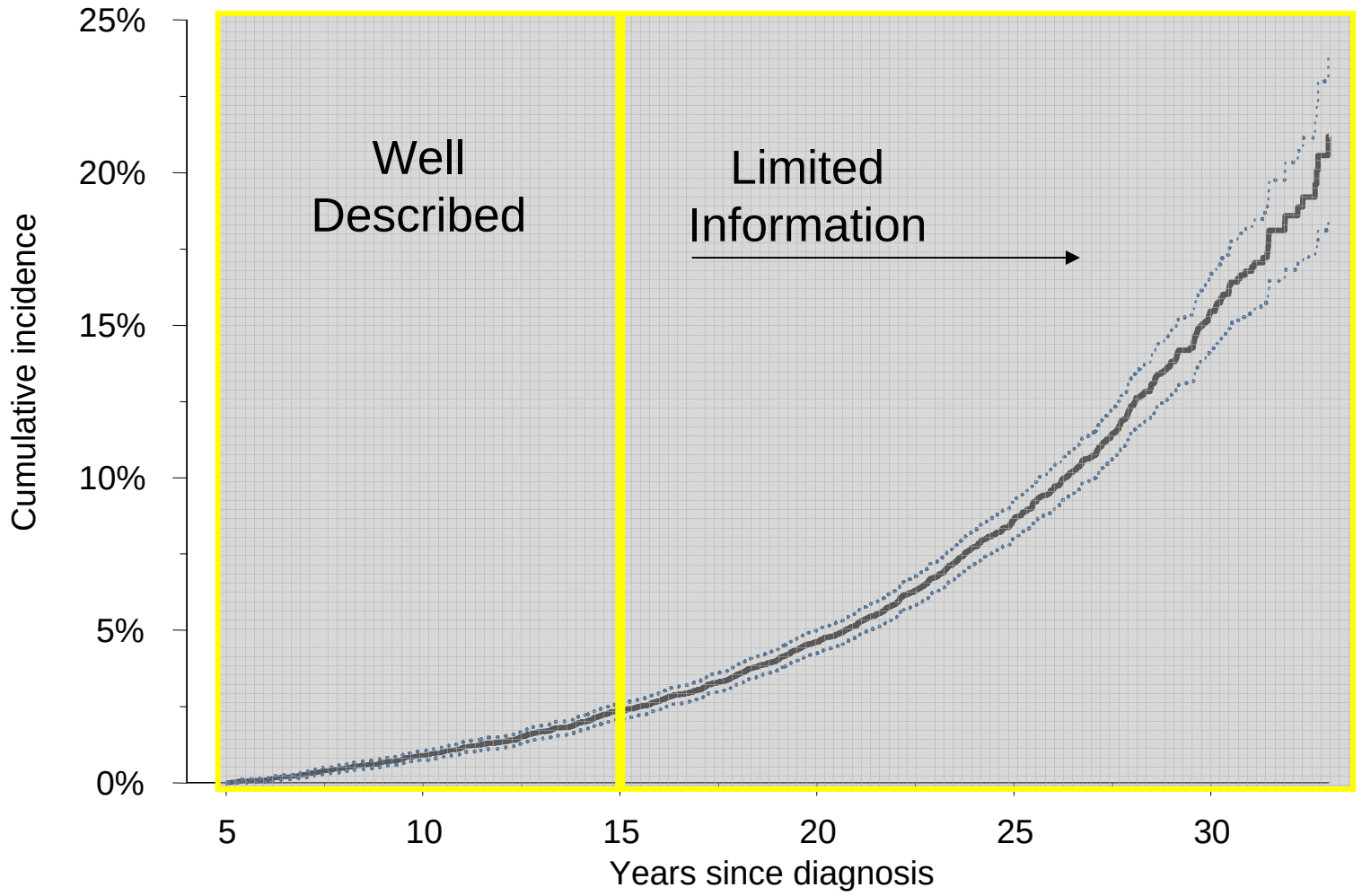




Perkins , et al., JCO, 2005

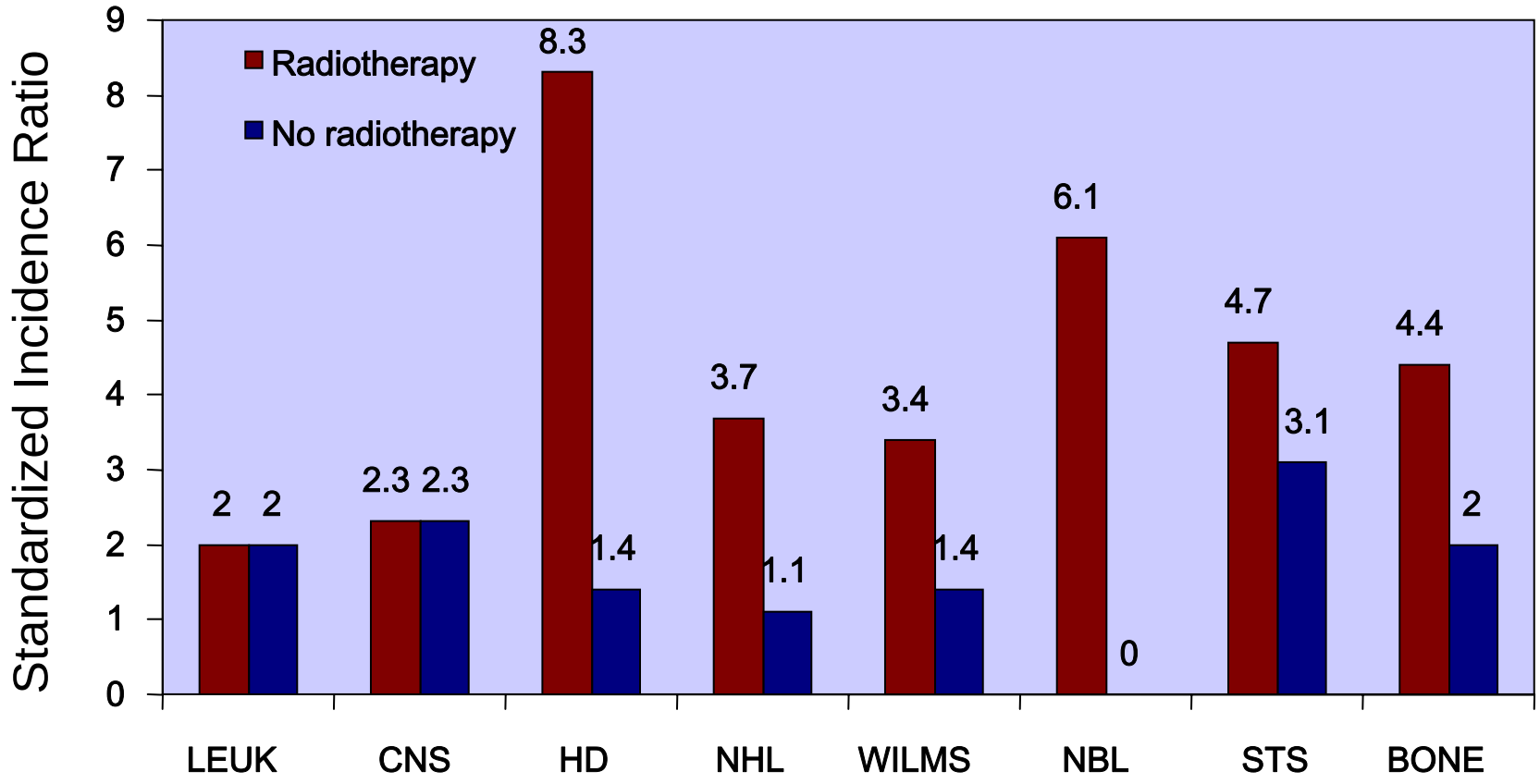
Malignancies Occurring 5+ years

Including Nonmelanoma Skin Cancer



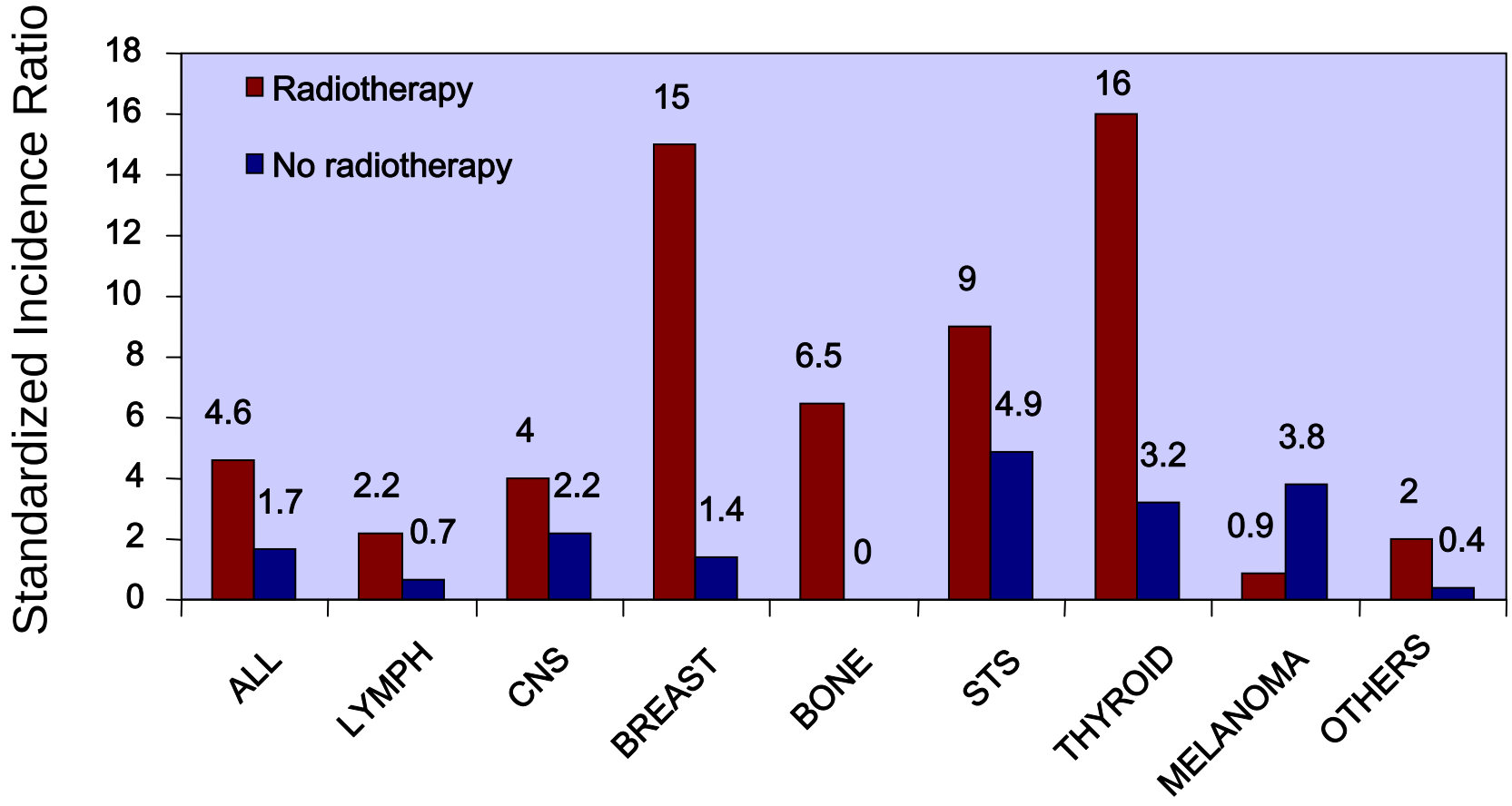
Second Malignancies occurring 15 or more years from Original Diagnosis

SIR by Primary Diagnosis and Radiotherapy



Second Malignancies Occurring 15 or more years from Original Diagnosis

SIR by Subsequent Neoplasm and Radiotherapy

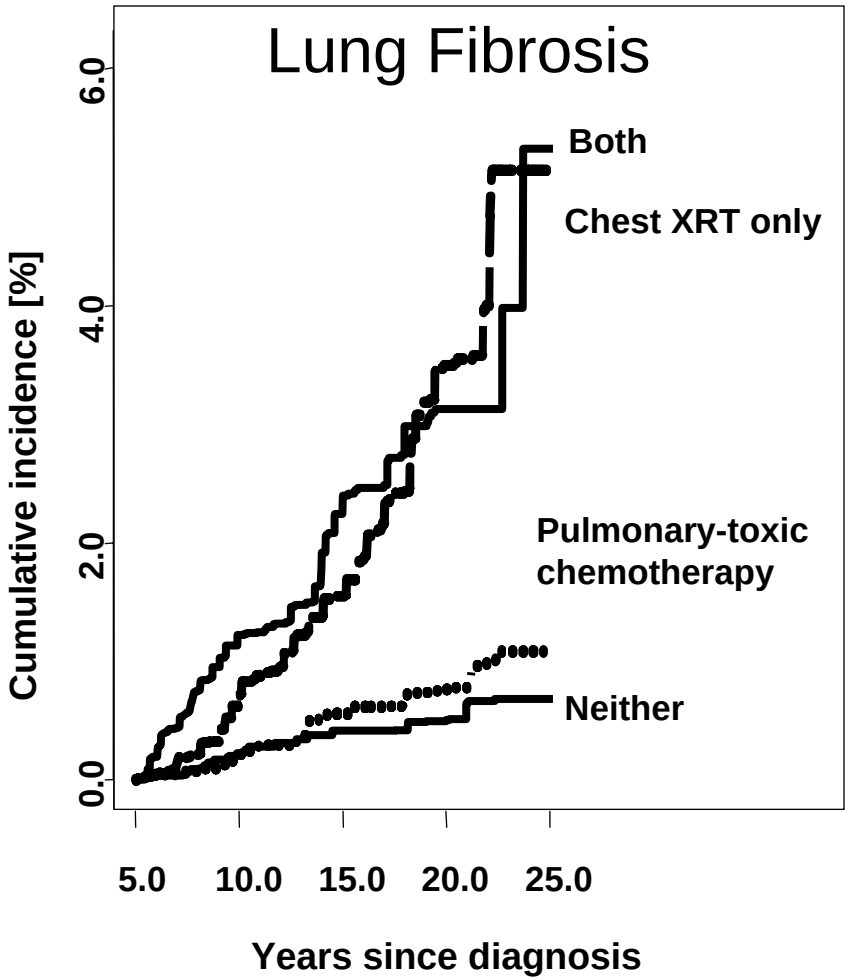


Chronic Health Conditions

Health Status Among 5+ Year Survivors

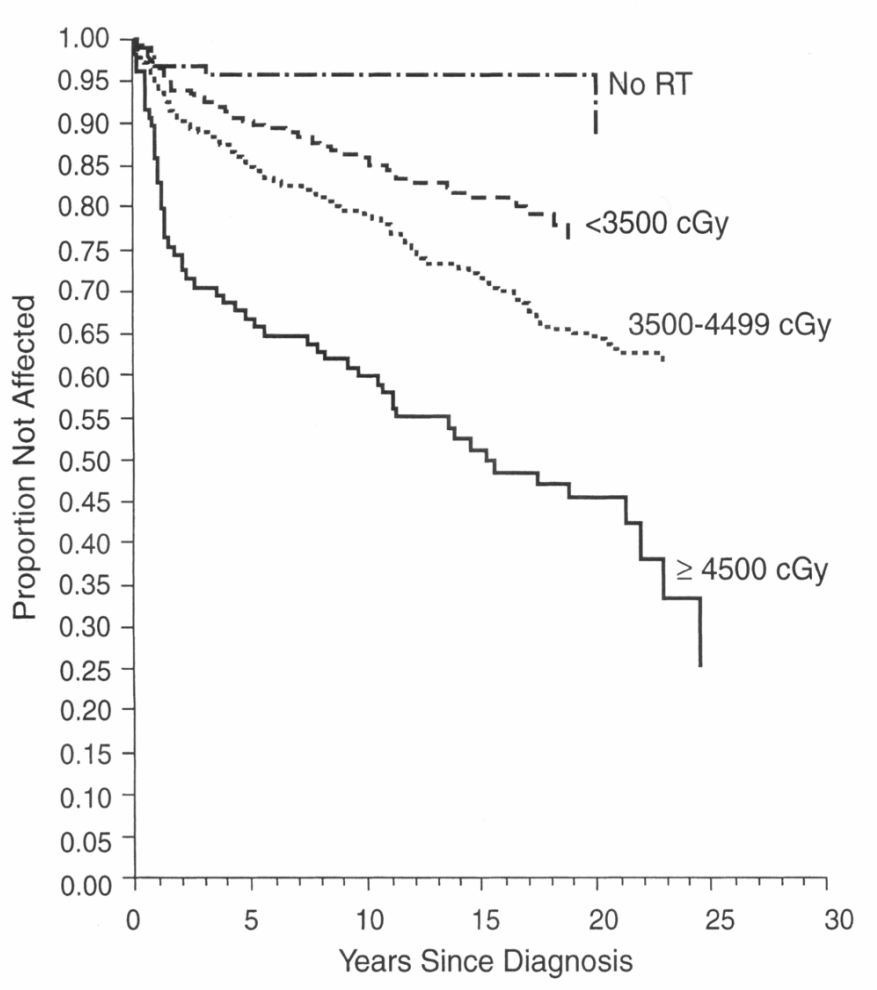
Health Domain	Survivors
General health	10.6%
Functional status	11.8%
Activity limitation	13.4%
Mental health	12.6%
Pain	10.2%
Anxiety/fears	13.2%
Any health domain	41.3%

Pulmonary Complications Among Childhood Cancer Survivors



- Five year survivors were 3.5-times more likely to be diagnosed with lung fibrosis, 5-times more likely to experience recurrent pneumonia, and 3-times more likely to require supplemental oxygen.
- Survivors treated with lung irradiation were 4.3-times more likely to have lung fibrosis.
- Cancer 2002; 95:2431-41

Thyroid Dysfunction Among Survivors of Hodgkin's Disease



- Among 1791 five year survivors of Hodgkin Disease, 34% were diagnosed with at least one thyroid abnormality.
- Hypothyroidism was the most common abnormality with a relative risk of 17.1 ($p<0.001$).
- Increasing dose of radiation to the thyroid, older age at diagnosis of Hodgkin disease, and female sex were all independently predictive of hypothyroidism.
- J Clin Endocrinol Metab 2000; 85:3227-32.

Assessment of Long-term Morbidity

- 10,397 survivors, diagnosed 1970-1986
- 3,034 siblings

Grading of conditions: CTCAE v3.0

Common Terminology Criteria for Adverse Events

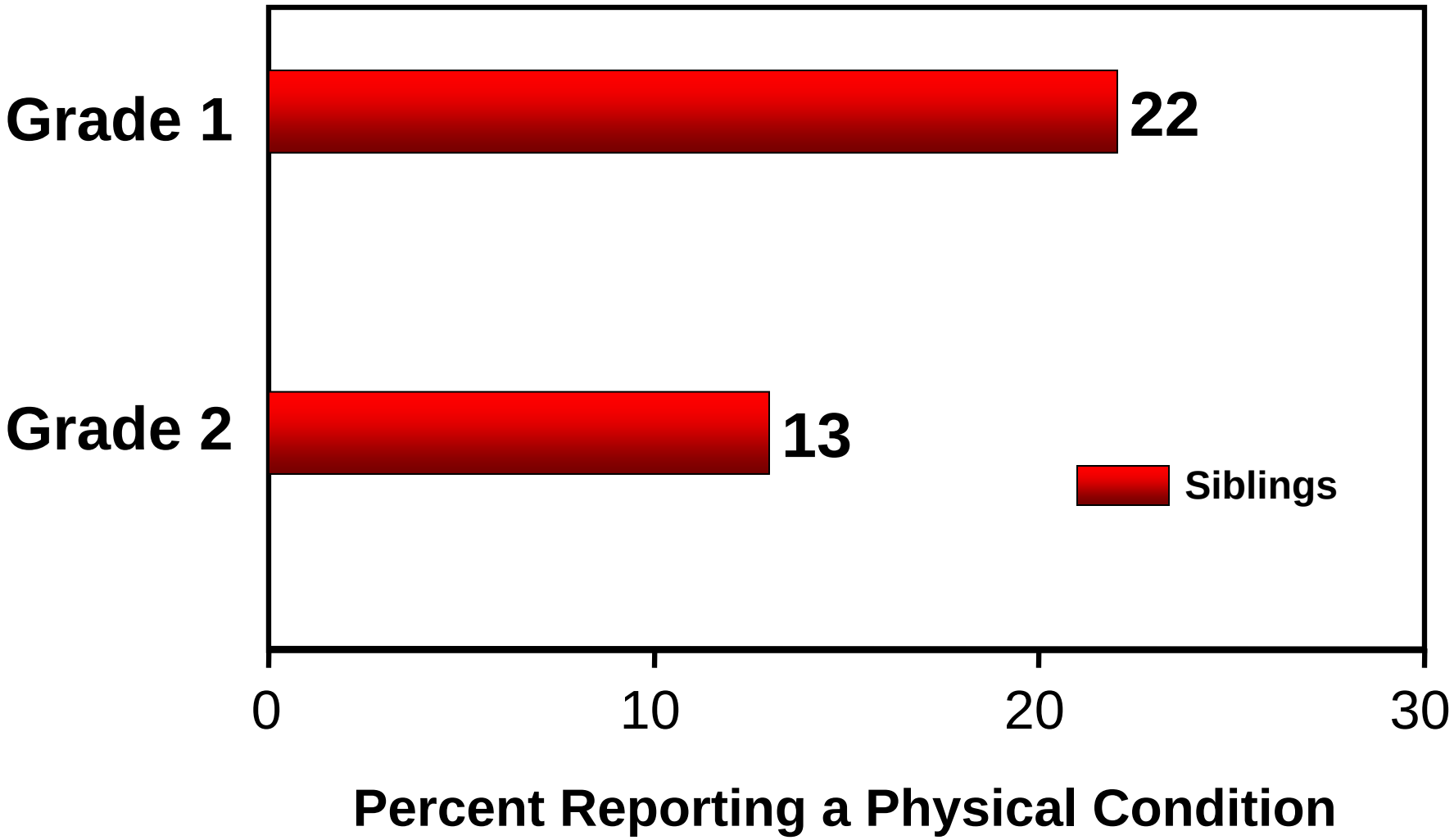
- Grade 1 Mild
- Grade 2 Moderate
- Grade 3 Severe
- Grade 4 Life-threatening or disabling
- Grade 5 Death

Assessment of Long-term Morbidity

Demographics

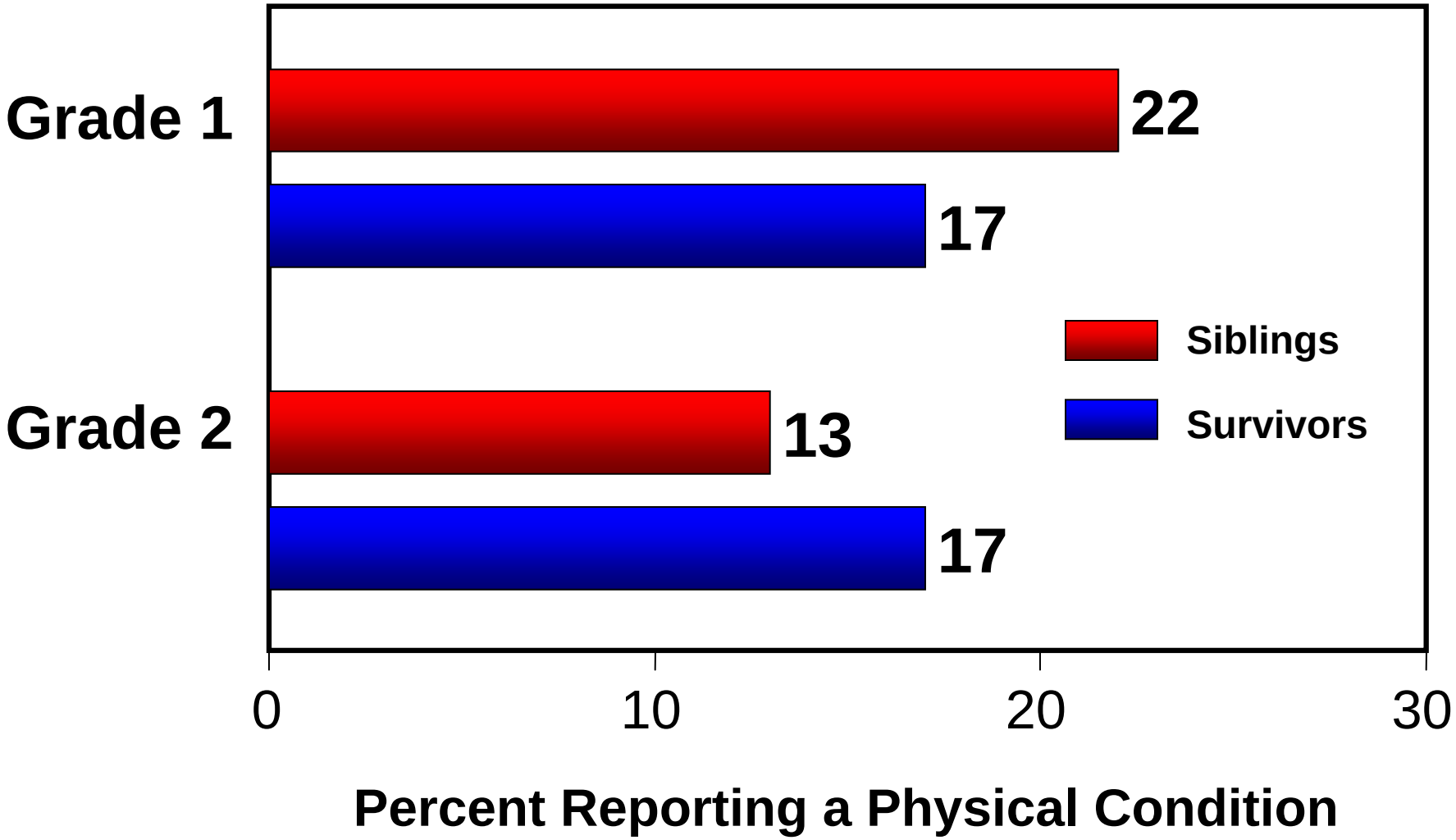
Characteristics	Survivors (N=10,397)	Siblings (N=3,034)
Gender: female	46%	53%
Race		
Non-Hispanic white	84%	92%
Minorities	16%	8%
Age at interview	27	29
Mean (range), years	(18 - 48)	(18 - 56)
Interval from cancer dx	18	
Mean (range), years	(6 - 31)	NA

Assessment of Long-term Morbidity



Assessment of Long-term Morbidity

Similar percentage with mild or moderate conditions



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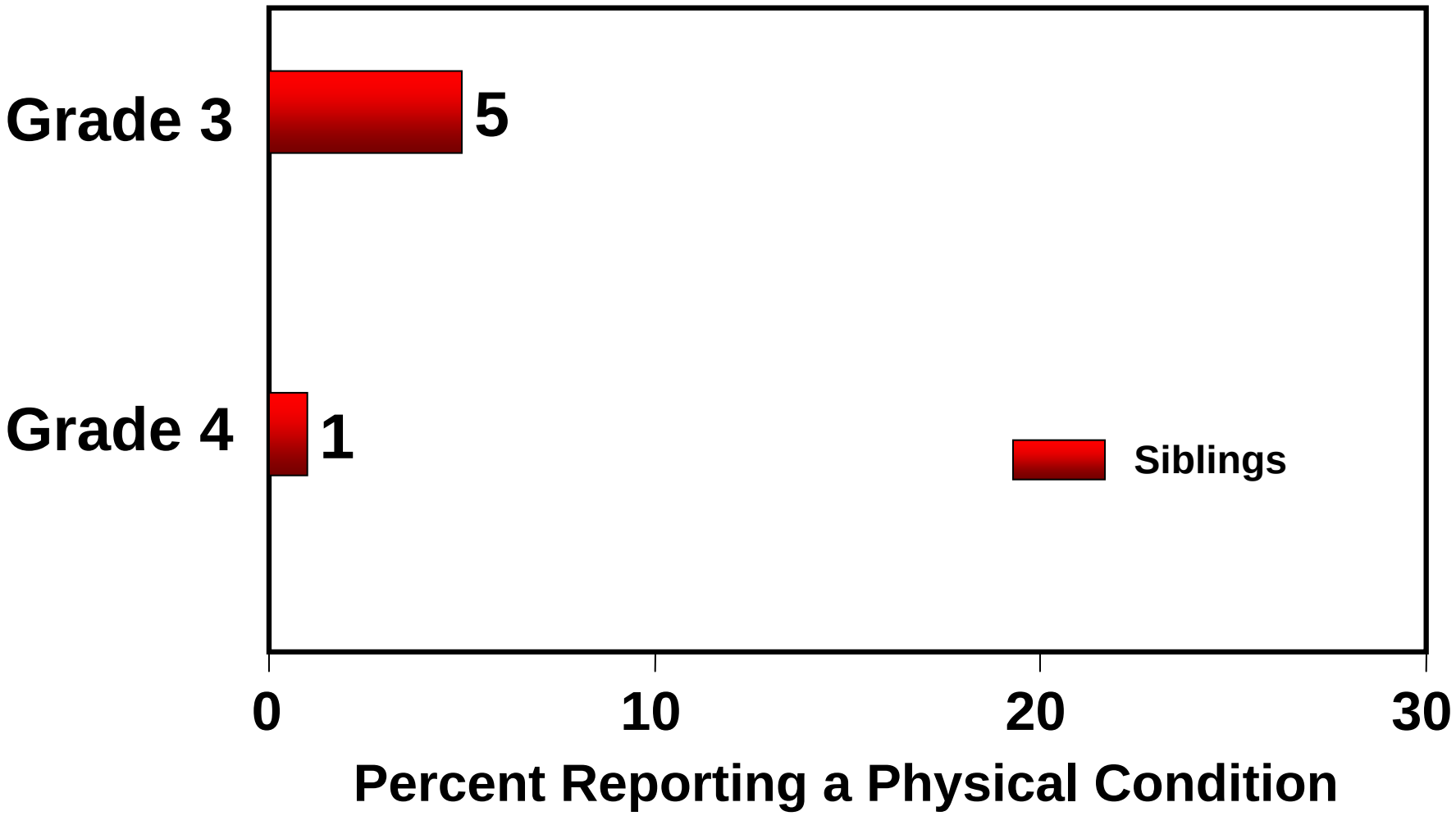
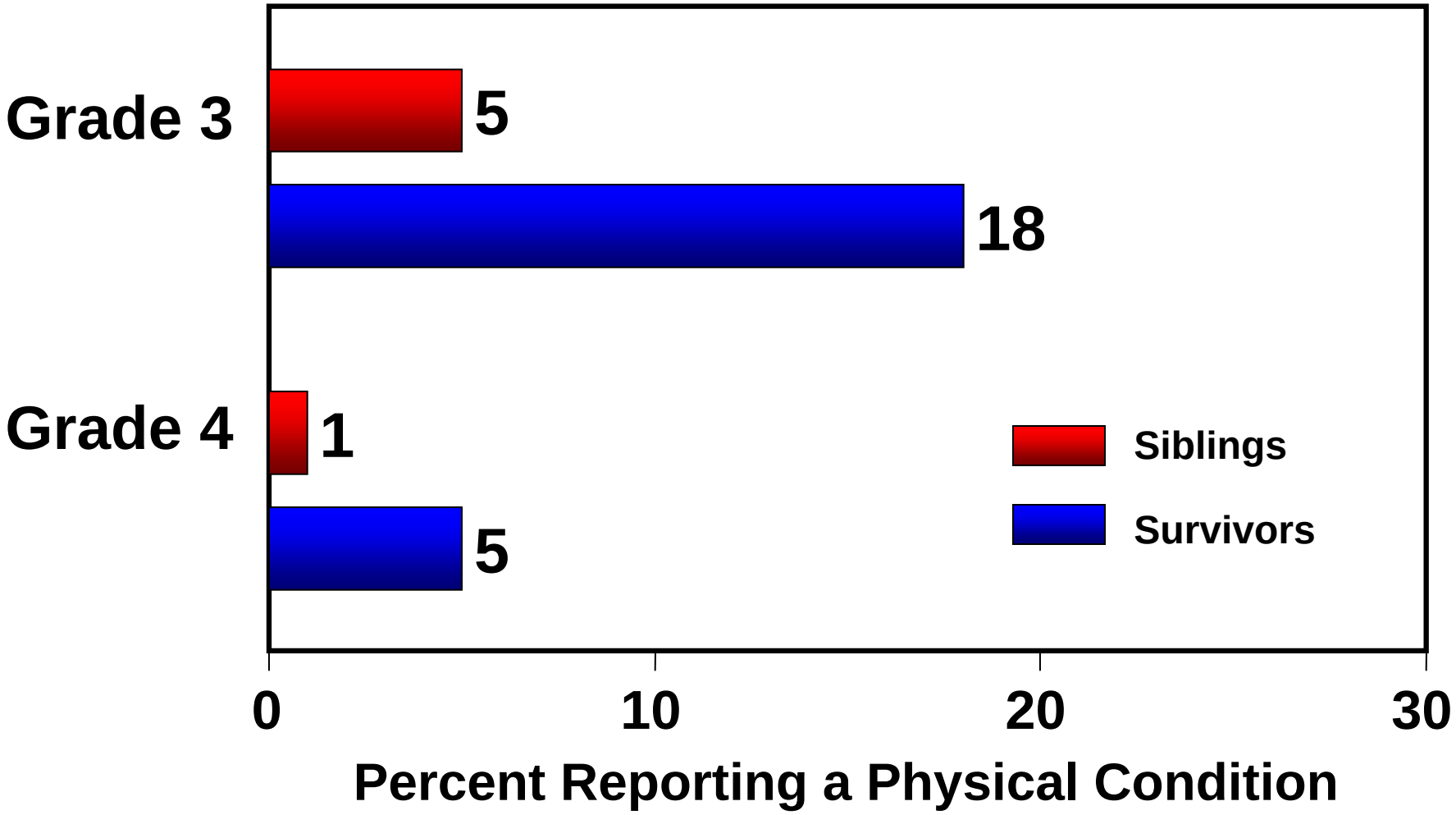
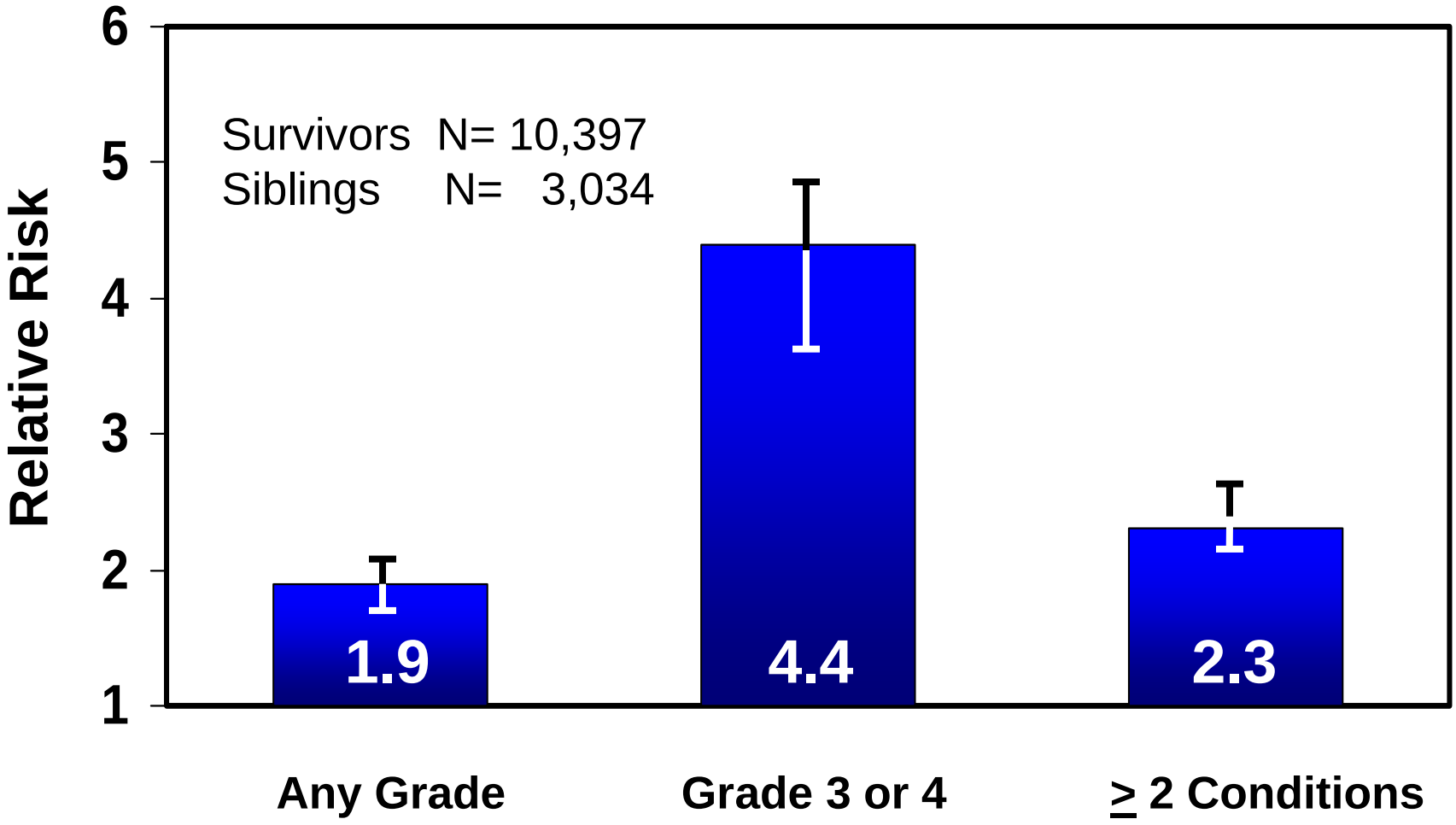


Assessment of Long-term Morbidity

Significant difference in severe/life-threatening conditions



Relative Risk* of Physical Health Conditions in Survivors Compared with Siblings



* Adjusted for age, sex, and race

Relative Risk* of Physical Health Conditions in Survivors Compared with Siblings

Primary Cancer	Any Grade	Grade 3 or 4	> 2 Conditions
Hodgkin	2.3	5.6	3.6
Bone tumor	1.4	5.5	1.2
CNS tumor	2.0	5.1	2.5
Wilms tumor	1.9	4.5	2.1
Sarcoma	1.7	4.4	1.9
Neuroblastoma	2.2	4.0	2.0
Leukemia	1.7	3.1	1.8
NHL	1.6	2.6	1.8

* Adjusted for age, sex, and race

Adjusted Relative Risk* of Physical Health Conditions in Survivors Compared with Siblings

Cancer Therapy	Any Grade	Grade 3 or 4	> 2 Conditions
No radiation	**1.4**	**2.4**	**1.3**
Any radiation	**2.1**	**5.1**	**2.7**
Brain RT	**1.9**	**4.4**	**2.3**
Chest RT	**2.5**	**6.2**	**3.7**
Abd RT	**2.4**	**6.3**	**3.3**
Pelvic RT	**2.6**	**7.5**	**3.8**
TBI	**3.0**	**5.4**	**3.8**

All risk estimates $p<0.001$

* Adjusted for age, sex, and race

Adjusted Relative Risk* of Physical Health Conditions in Survivors Compared with Siblings

Cancer Therapy	Any Grade	Grade 3 or 4	> 2 Conditions
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Any radiation	2.1	5.1	2.7
Brain RT	1.9	4.4	2.3
Chest RT	2.5	6.2	3.7
Abd RT	2.4	6.3	3.3
Pelvic RT	2.6	7.5	3.8
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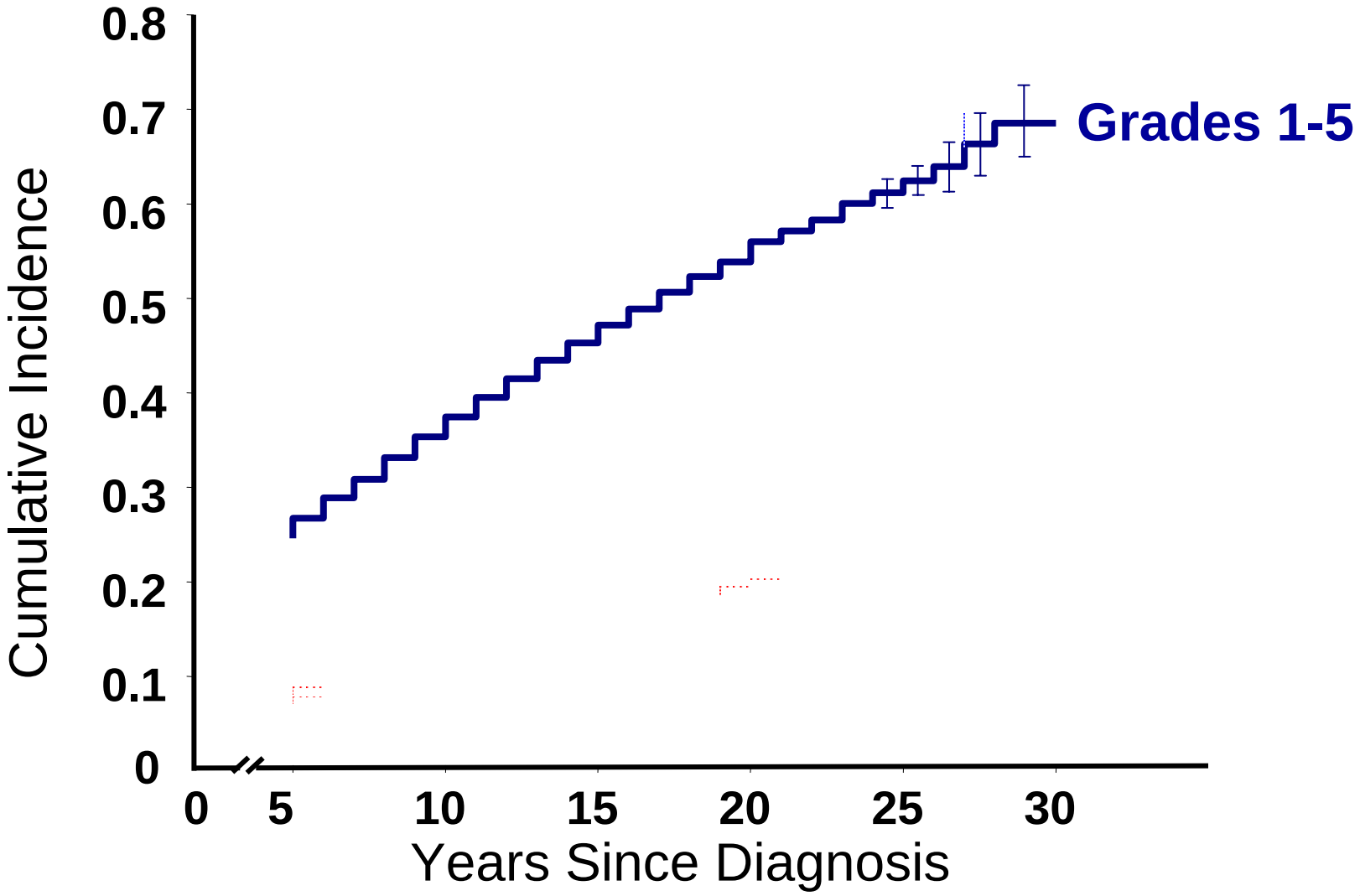
Cumulative Incidence of Physical Health Conditions Among 10,397 Long-term Survivors



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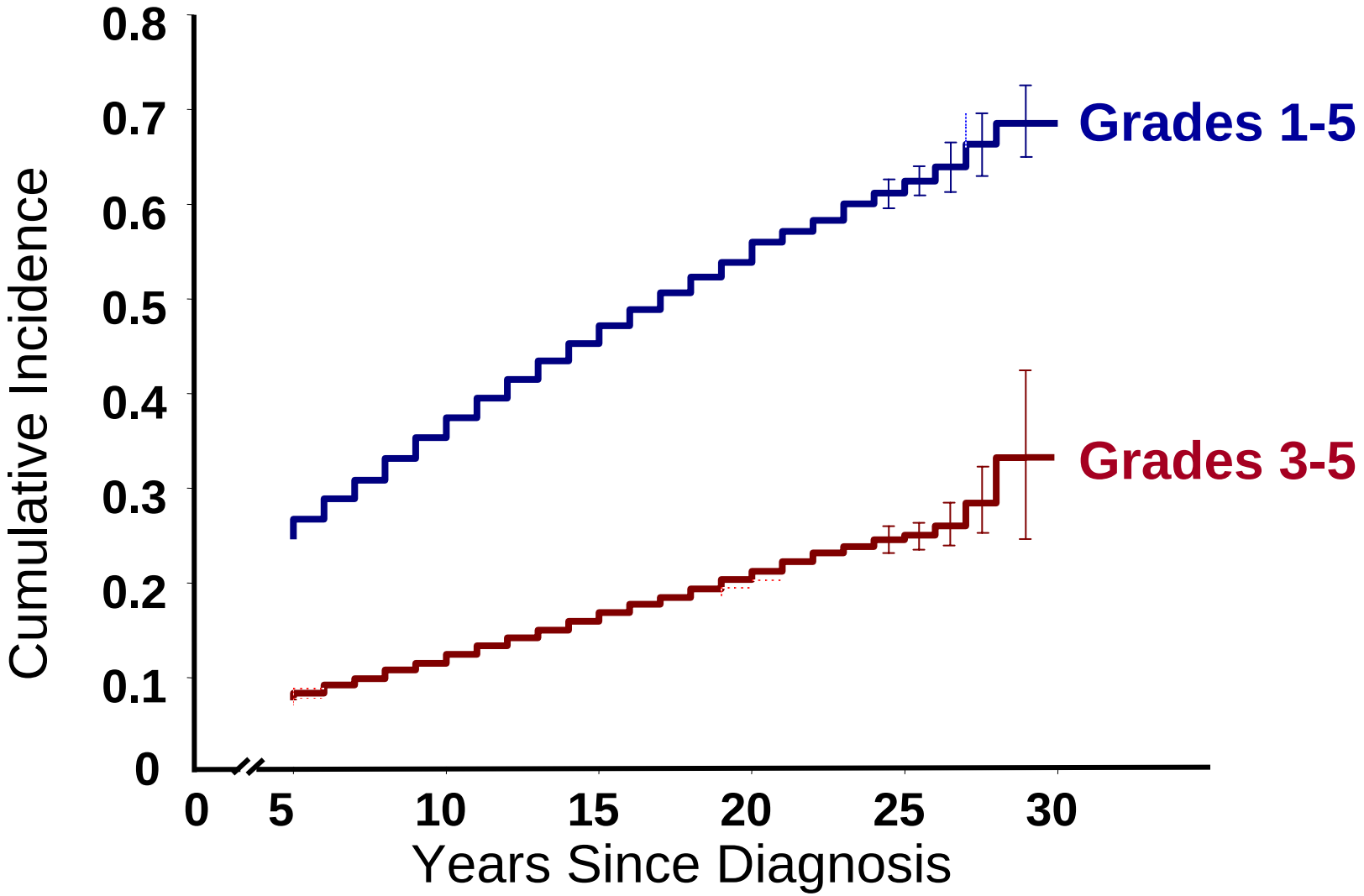
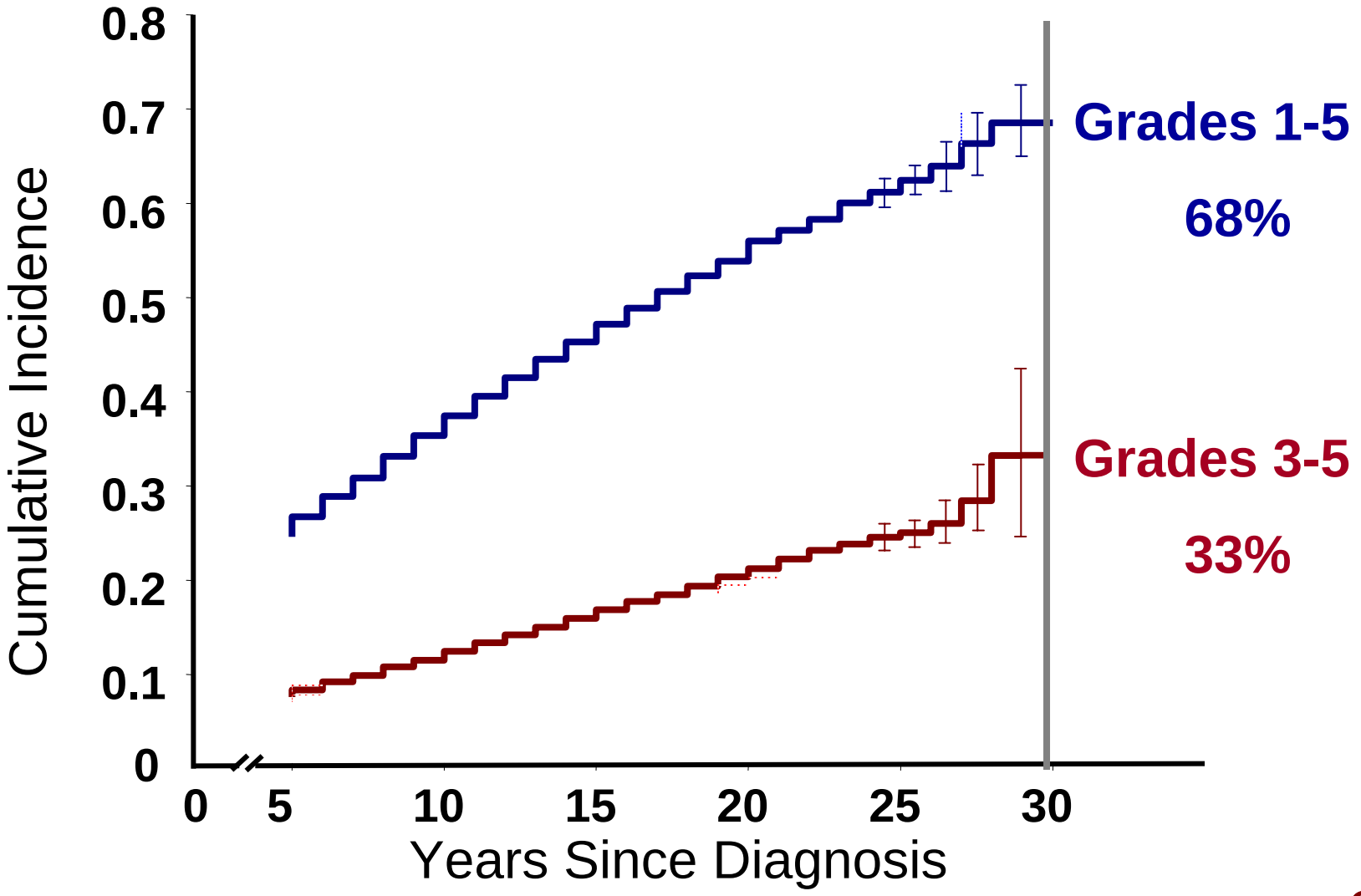
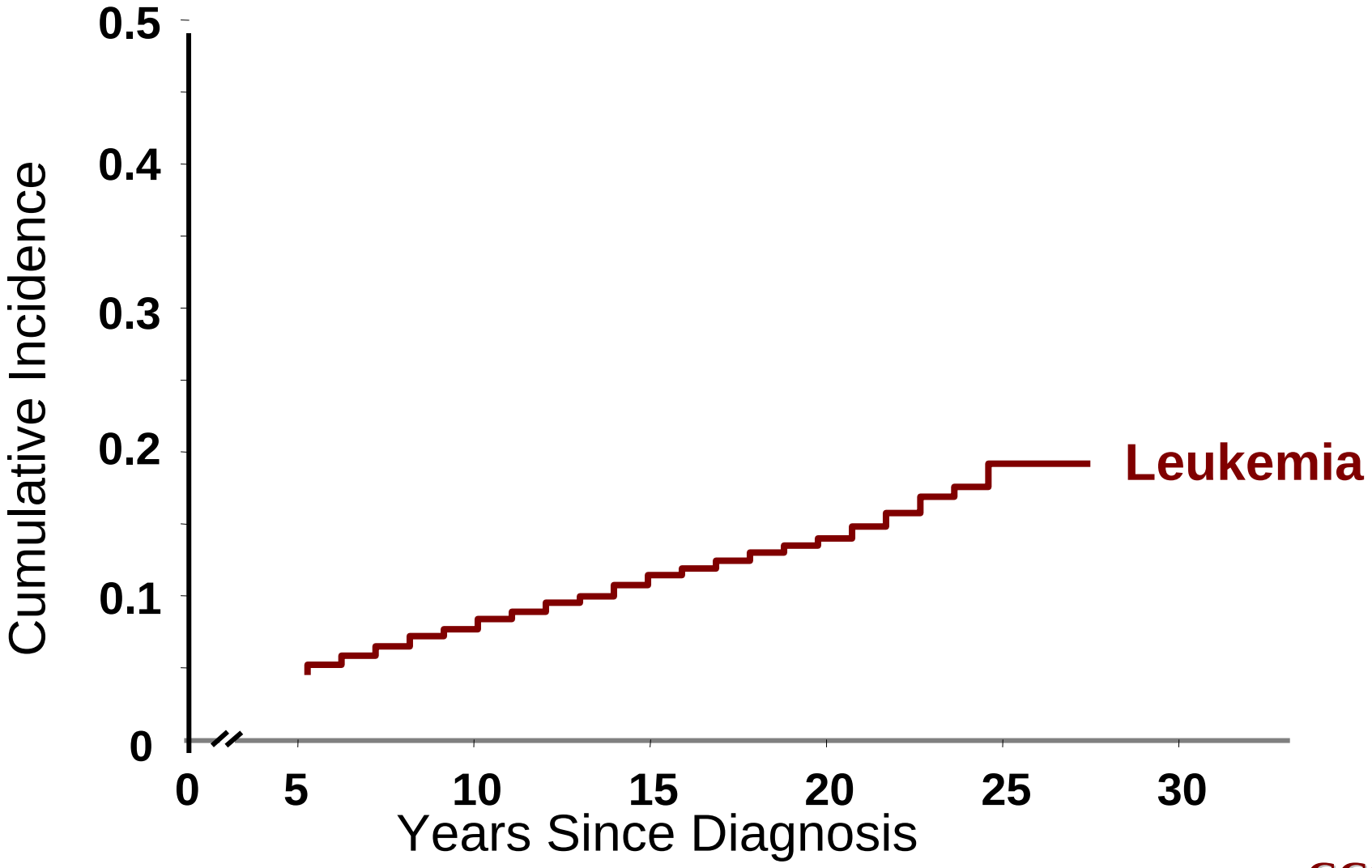


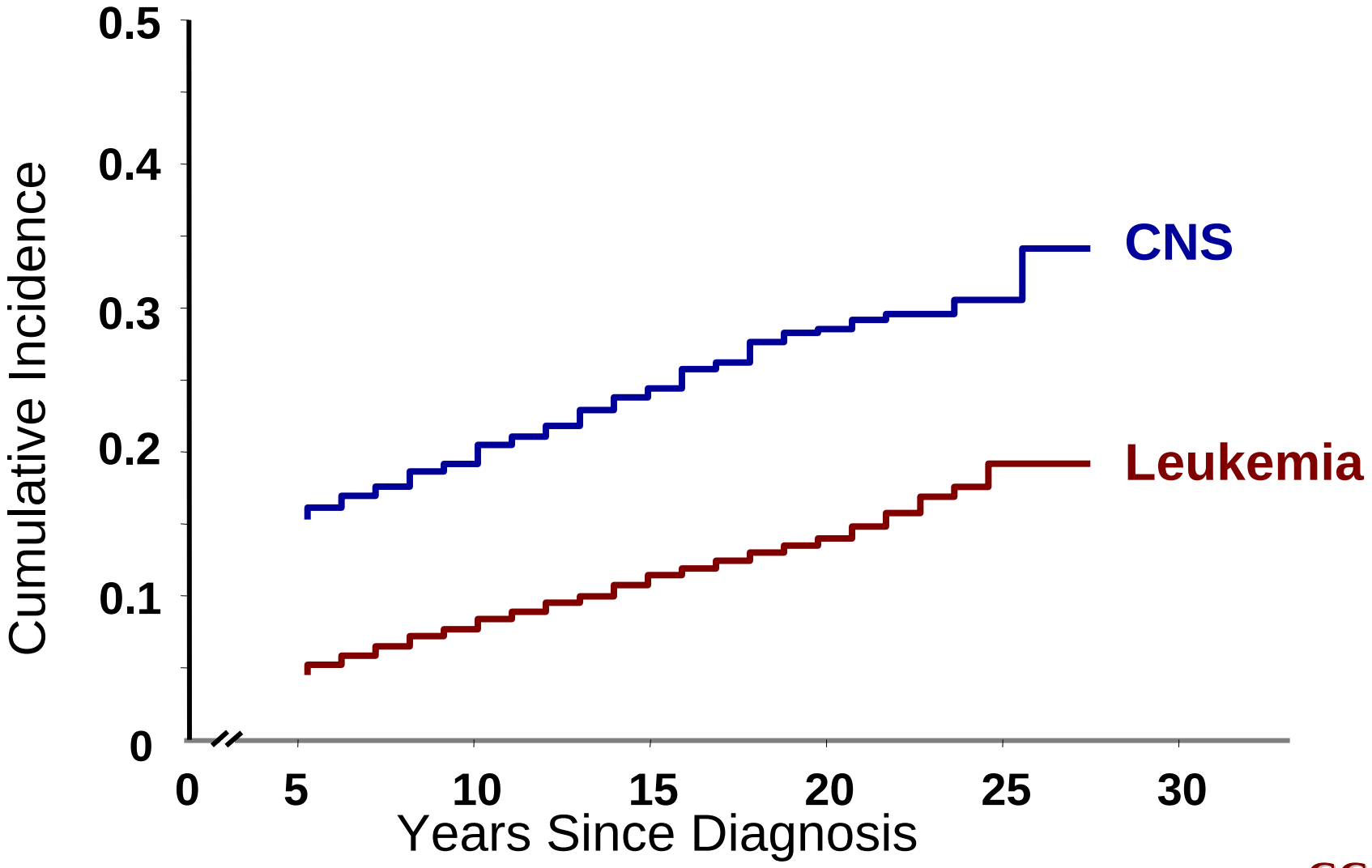
Cumulative Incidence of Physical Health Conditions Among 10,397 Long-term Survivors



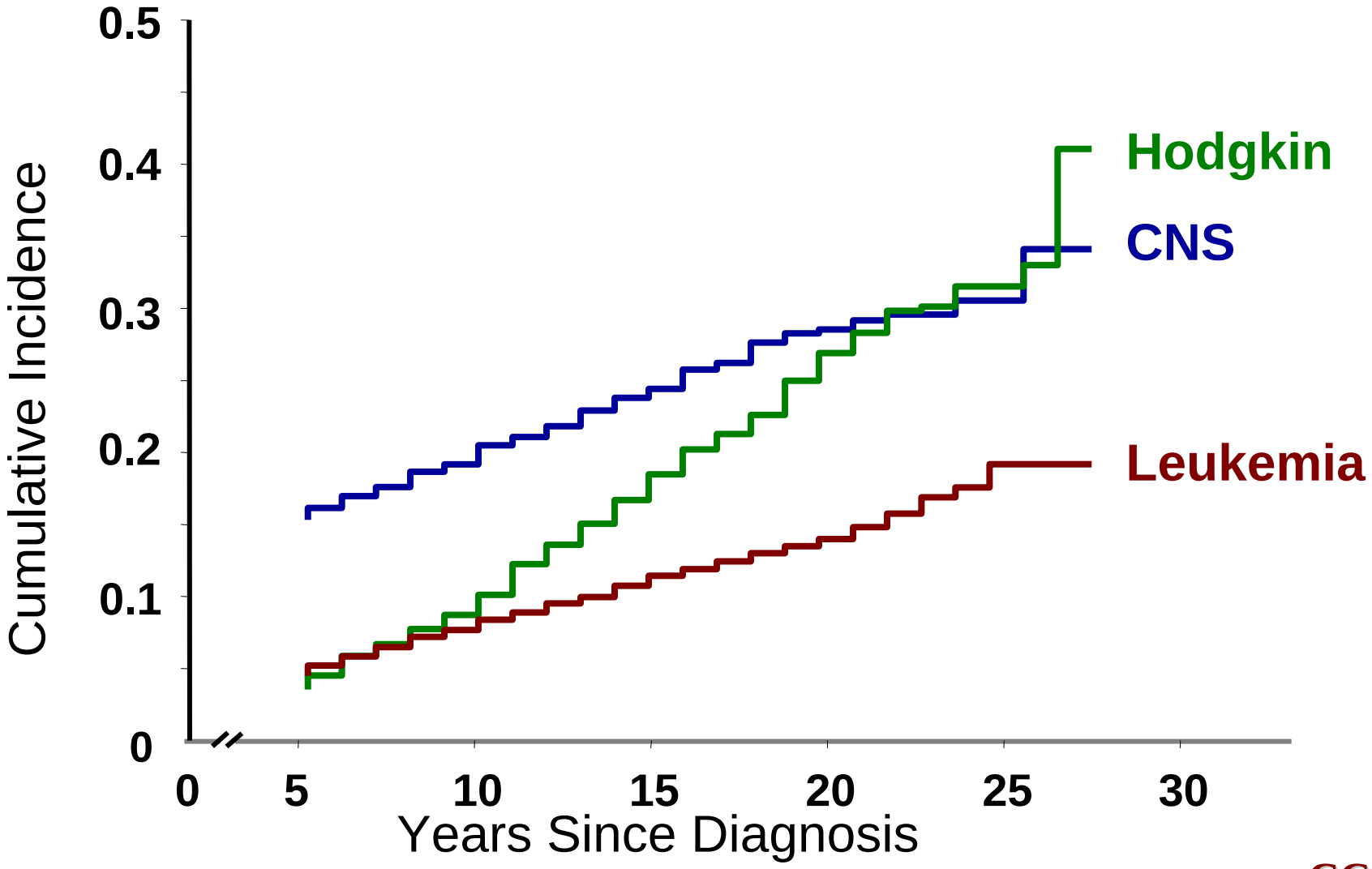
Cumulative Incidence of Grade 3 or 4 Physical Health Conditions



Cumulative Incidence of Grade 3 or 4 Physical Health Conditions



Cumulative Incidence of Grade 3 or 4 Physical Health Conditions



Assessment of Long-term Morbidity Among 5+ Year Survivors (n=10,397)

- By 30 years post cancer:
  - 68% survivors with at least one condition
  - 33% with a grade 3-5 condition
  - 31% with multiple conditions

- Survivors - 4.4 times more likely to have a severe or life-threatening health condition than siblings

Tobacco Use

Smoking Among Survivors

- 9709 Survivors 18 years of age or older at time of enrollment in CCSS
- Smoker defined as 100+ cigarettes lifetime (self-report)
    - Age at onset of smoking
    - Average number of cigarettes smoked
    - Total number of years smoked
    - Quit attempts
    - Age at cessation for former smokers
- Use of tobacco products other than cigarettes

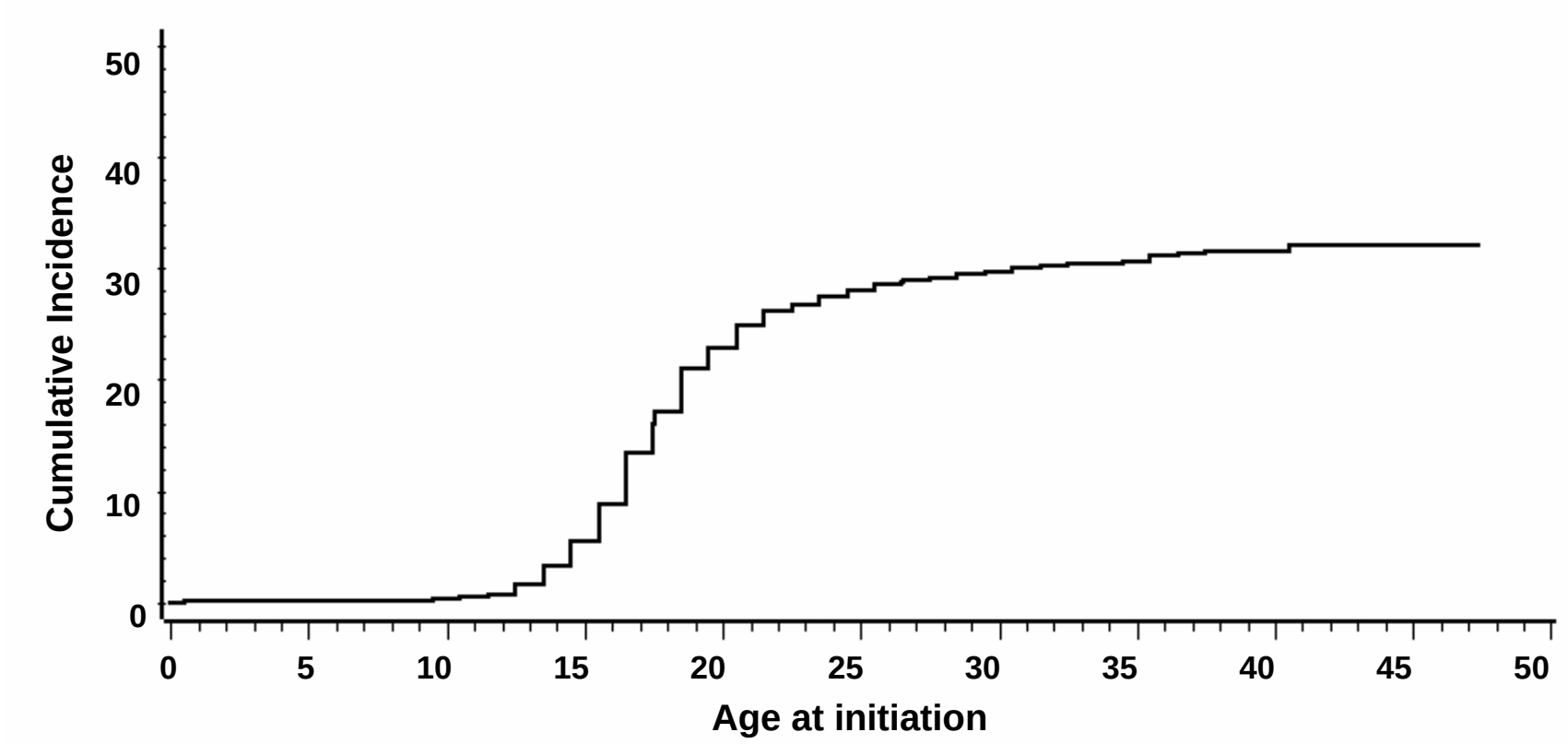
Smoking Among Survivors

- 28% reported ever smoking
- 17% were current smokers
- Expected rate of self-reported smoking calculated using age-, sex- and race-specific data from the National Health Interview Survey (1993)

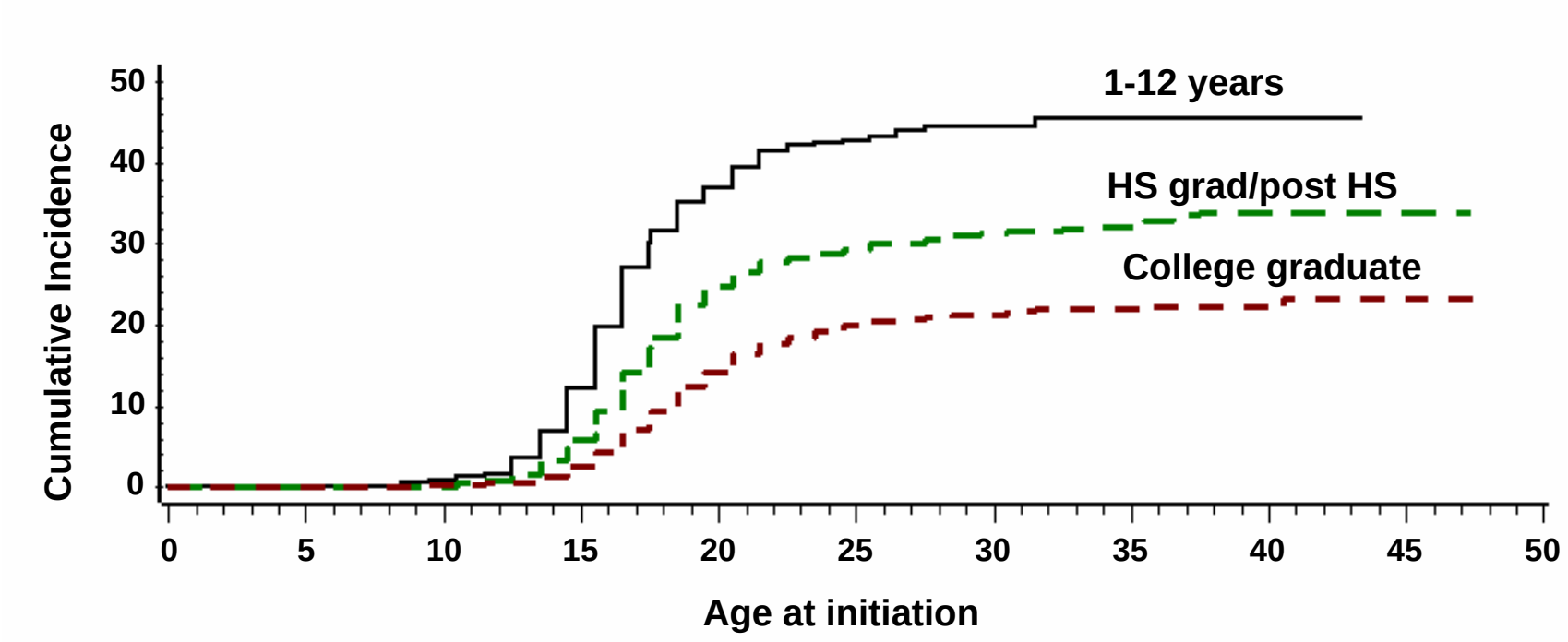
- Observed : Expected Ratio (95% Confidence Intervals)

	Smoking Initiation	Smoking Cessation
Overall	**0.72 (0.69 - 0.75)**	**1.22 (1.15 - 1.30)**
Males	**0.73 (0.69 - 0.77)**	**1.17 (1.07 - 1.28)**
Females	**0.70 (0.66 - 0.74)**	**1.29 (1.17 - 1.41)**

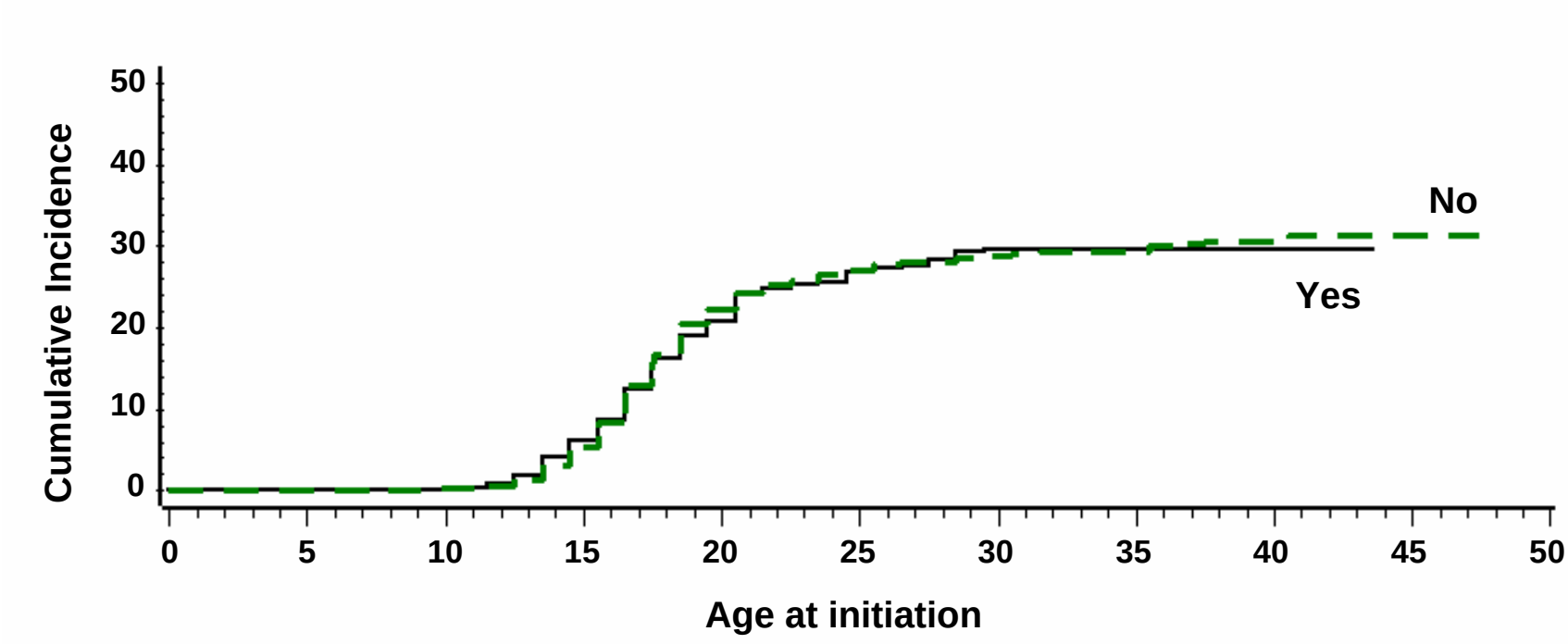
Age at Initiation of Smoking
Entire Cohort



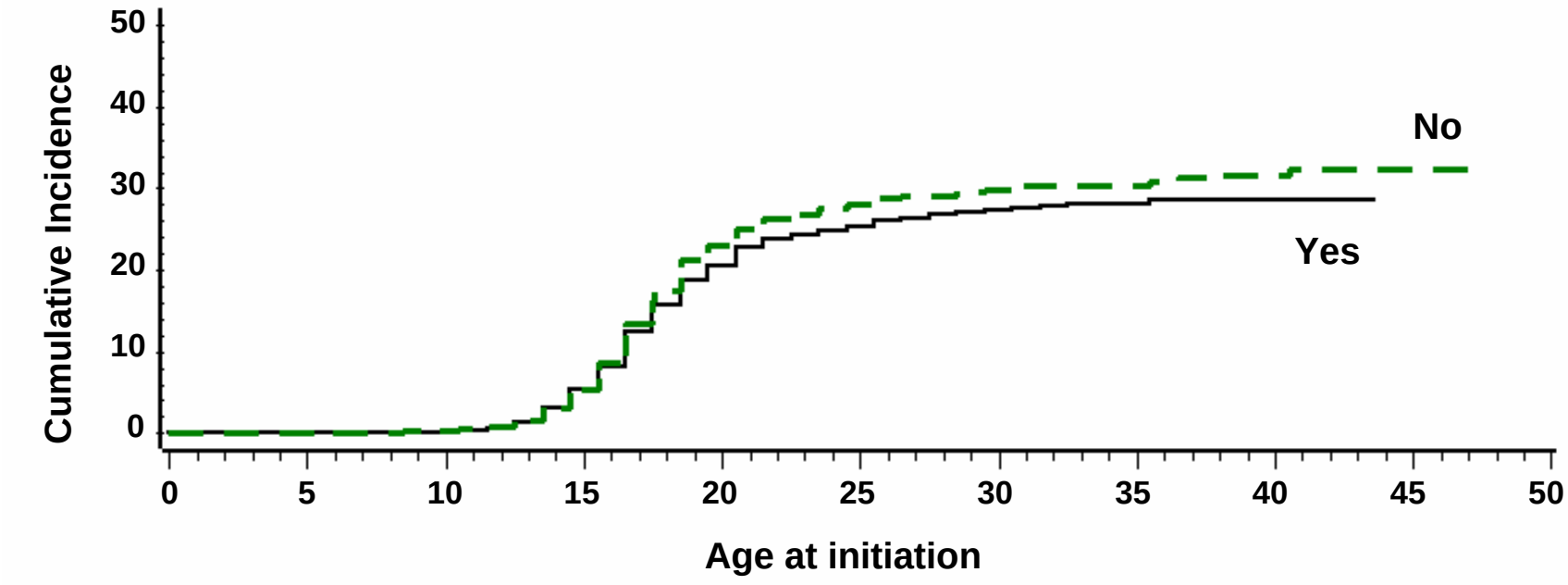
Age at Initiation of Smoking by Education



Age at Initiation of Smoking by Cancer Treatment - Bleomycin



Age at Initiation of Smoking by Cancer Treatment - Anthracyclines



Body Mass Index

Obesity in ALL Survivors

Background

- Obesity in childhood, adolescence, and young adulthood is an important predictor of Type 2 Diabetes, Hypertension, dyslipidemia, and ultimately CVD

- Risk of death from all causes, CVD, and cancer increases throughout the ranges of being overweight and obese

Obesity in Acute Lymphoid Leukemia Survivors

Study Population

1,765 adult survivors of childhood ALL

- Age (mean) – 24.1 yrs (range 18-48)
- Age at DX (mean) – 7.5 yrs (0.1-20.8)
- Interval from DX (mean) – 17.1 yrs (7.4-27.5)
- 49% females
- 89.8% white, non-Hispanics

Obesity in Acute Lymphoid Leukemia Survivors

Outcome Measures

Self-reported heights and weights:

- BMI (kg/m^2)
- Overweight BMI 25.0 – 29.9
- Obese BMI $\geq$ 30.0
- Primary outcome: 3-level polytomous variable (normal, overweight, obese)

Obesity in Acute Lymphoid Leukemia Survivors

Results

CRT ≥ 20 Gy (N=841)

Age- and race-adjusted OR for obesity:

- Females 2.59 95% CI – 1.88-3.55
- Males 1.86 95% CI – 1.33-2.57

Obesity in Acute Lymphoid Leukemia Survivors

Results

Age at diagnosis modifies effect with CRT ≥ 20 Gy

Females:		OR	95% CI
Age at DX	0-4	3.81	2.34-5.99
	5-9	2.30	1.39-3.59
	10-14	2.16	1.11-3.61
	15-21	0.88	0.00-2.63

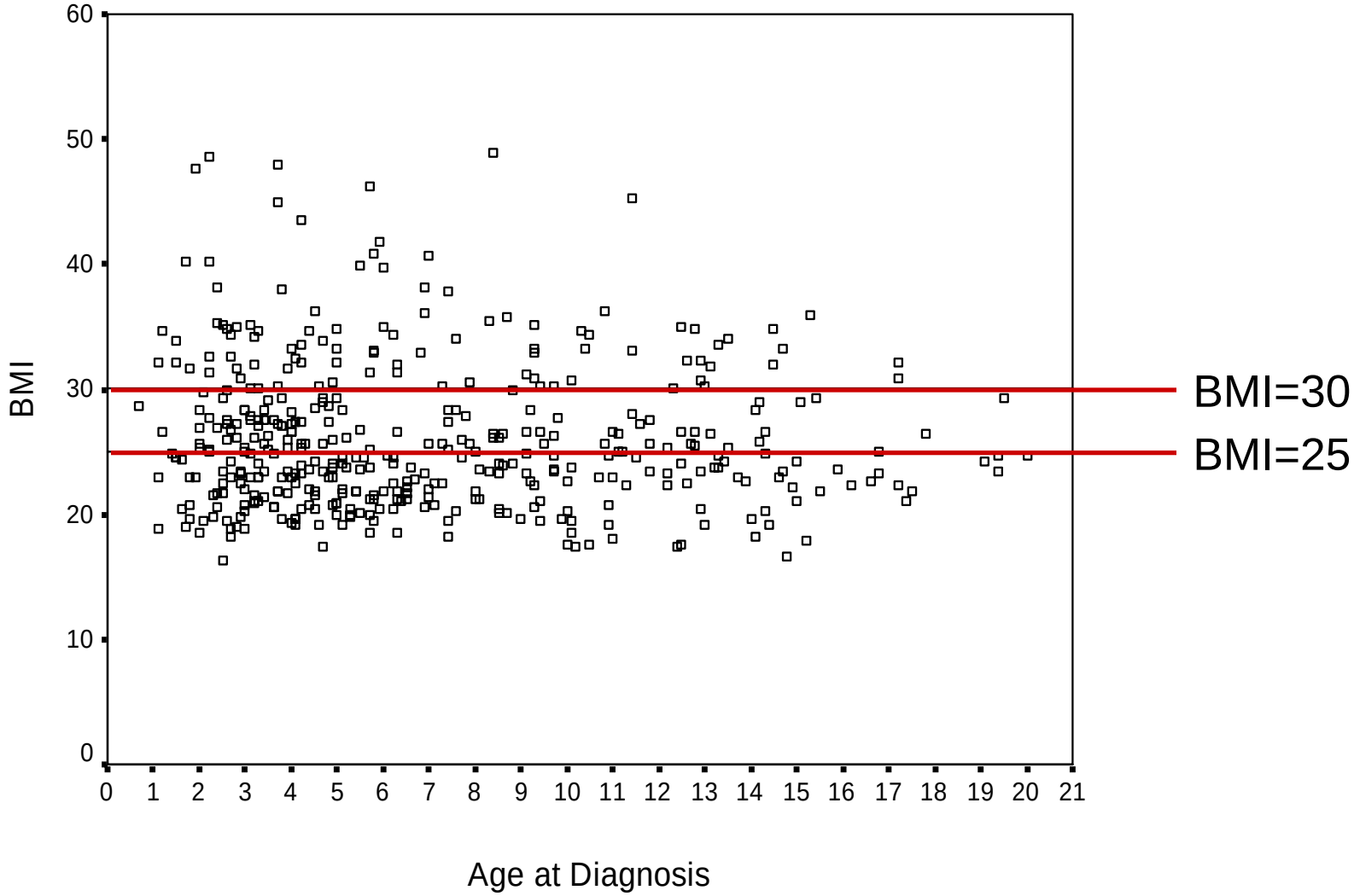
Obesity in Acute Lymphoid Leukemia Survivors

Results

Age at diagnosis modifies effect with CRT ≥ 20 Gy

Males:		OR	95% CI
Age at DX	0-4	2.15	1.31-3.38
	5-9	1.93	1.07-3.28
	10-14	2.02	1.00-4.13
	15-21	0.71	0.00-1.92

Scatterplot for unadjusted BMI by age at diagnosis for females treated with ≥ 20 Gy CRT



Obesity in Acute Lymphoid Leukemia Survivors

Future Considerations

- Investigate mechanisms of possible causation
- Further evaluation of more recent protocols
- Strategies to encourage longitudinal follow-up of ALL survivors treated with CRT $\geq$ 20 Gy to:
  - Promote weight loss/maintenance
  - Screen for co-morbid risk factors
  - Increase levels of physical activity

Long-Term Survivors of Childhood ALL

LEPTIN RECEPTOR POLYMORPHISM (Gln223Arg) AND OBESITY

- Leptin is adipocyte-derived hormone that binds to receptors in the hypothalamic-pituitary axis
- Arg allele in the Gln223Arg polymorphism is associated with decreased leptin binding affinity
- Carriers of Arg allele have increased serum leptin levels and increased body mass index
- Inconsistency exist in the literature regarding the associations of Arg and serum leptin and/or BMI

Long-Term Survivors of Childhood ALL

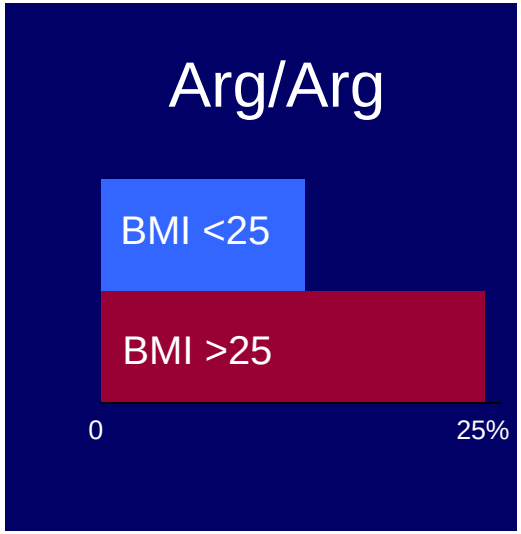
LEPTIN RECEPTOR POLYMORPHISM (Gln223Arg) AND OBESITY

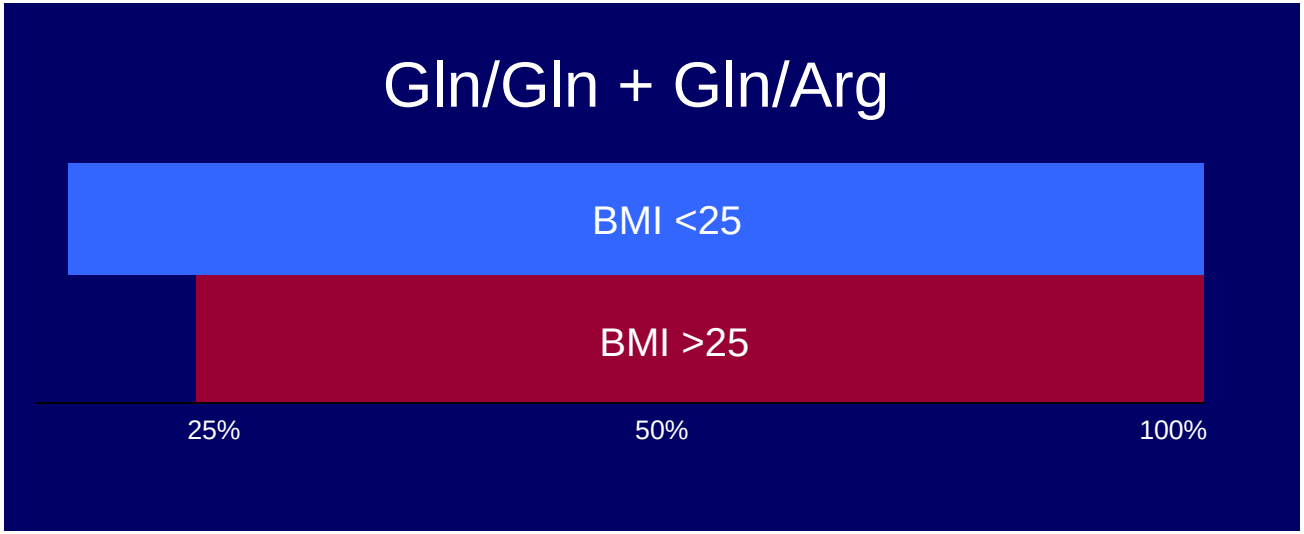
Hypotheses:

- Leptin receptor polymorphism Gln223Arg influences susceptibility to obesity among adults who are long-term survivors of childhood ALL
- An interaction exists between presence of Arg allele and high dose cranial radiation in predicting obesity among adults.

Risk of BMI >25 (Overweight or Obese) in 294 Female Childhood ALL Survivors

Leptin Receptor Polymorphism Gln223Arg





Arg/Arg

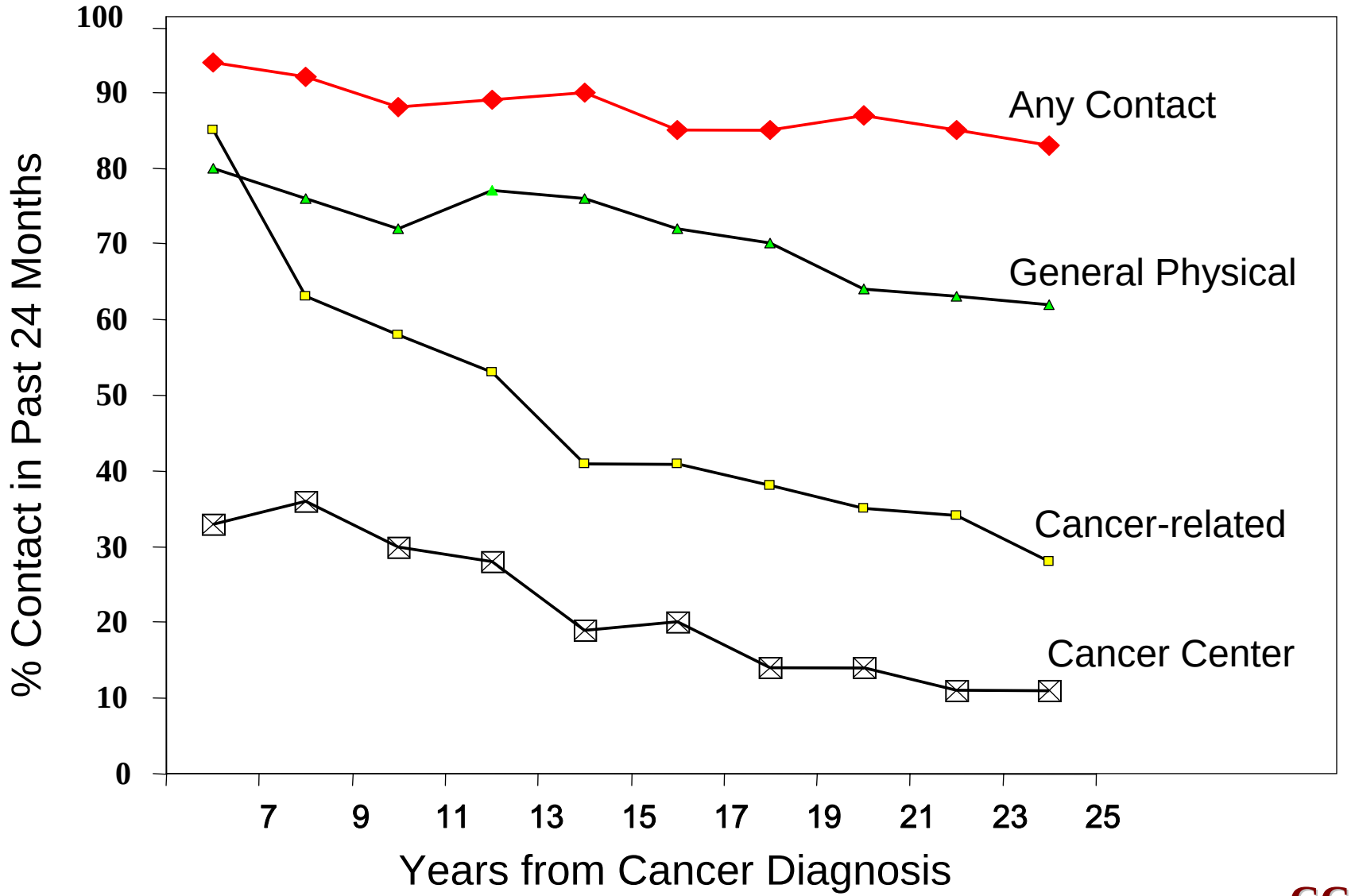
$OR_{(adj)}$ = 2.5
(95% CI = 1.3 – 4.8)
P = 0.004

Arg/Arg x RT

OR = 6.1
(95% CI = 2.1 – 22.0)
$P_{(inter)}$ = 0.04

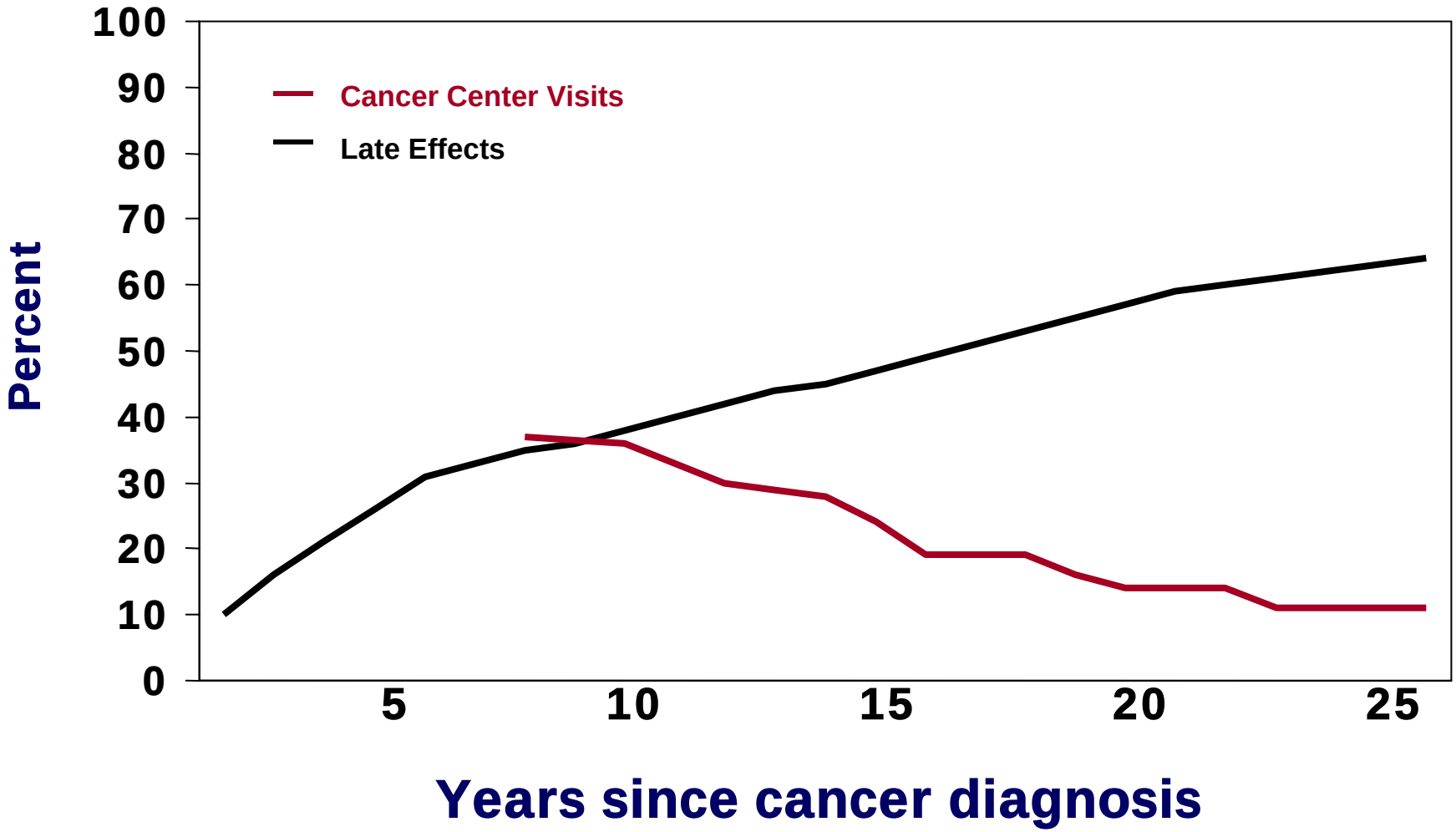
Follow-up and Health Care

Health Care Utilization in 5+ Year Survivors

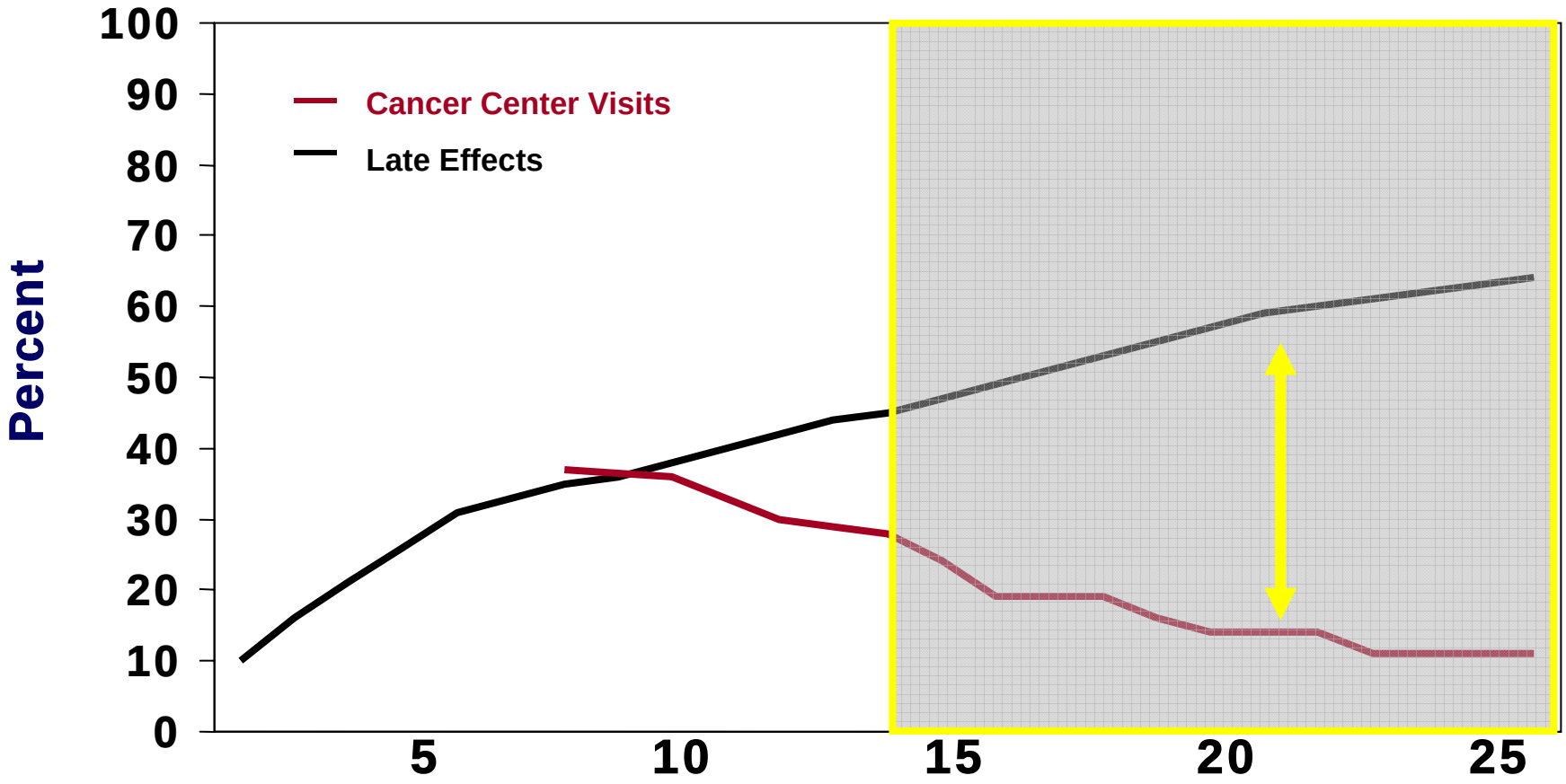


Oeffinger et al, 2003

Cancer Center Visits and Late Effects



Cancer Center Visits and Late Effects



St. Jude ACT Clinic

- **A**fter **C**ompletion of **T**herapy Clinic
- Multi-disciplinary team
- Research within a clinical care setting
- Established in 1984 to address the medical and psychosocial needs of childhood cancer survivors
- Mission: To improve quality of life of long-term childhood cancer survivors
- Fully funded by the American Lebanese Syrian Associated Charities (ALSAC)

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

ACT Statistics

- 5187 five-year survivors
- 1357 ACT patients
- 3830 Alumni survivors
- 1890 St. Jude clinical encounters over past year

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

Goals of After Therapy Care

- To maintain cancer-free survival.
- To prevent, reduce, or correct cancer-related complications.
- To detect cancer-related complications at early stages.
- To optimize health and QOL.

SJCRH – Lifetime Cohort

- Recruit 2500 alumnus of ACT
- Re-initiate ongoing clinical follow-up at SJCRH
- Frequency of follow-up determined by risk- and research-based criteria
- Primary objective is research
- Provide outstanding clinical assessment
- Criteria and characteristics to be established
- Serve as source for interventional research

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Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 2.0 – March 2006

CureSearch

Children's Oncology Group

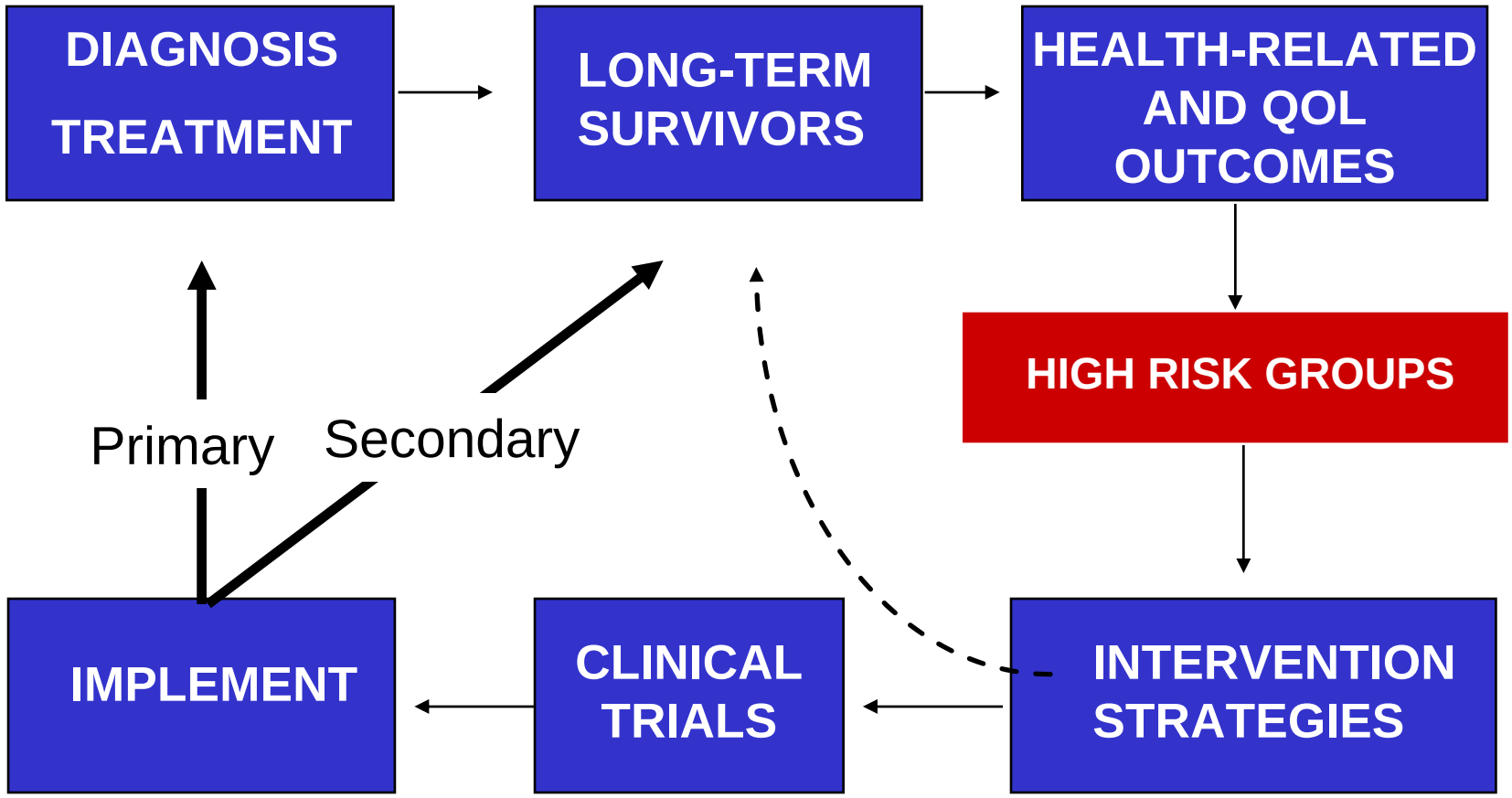
www.survivorshipguidelines.org

Key Content Areas

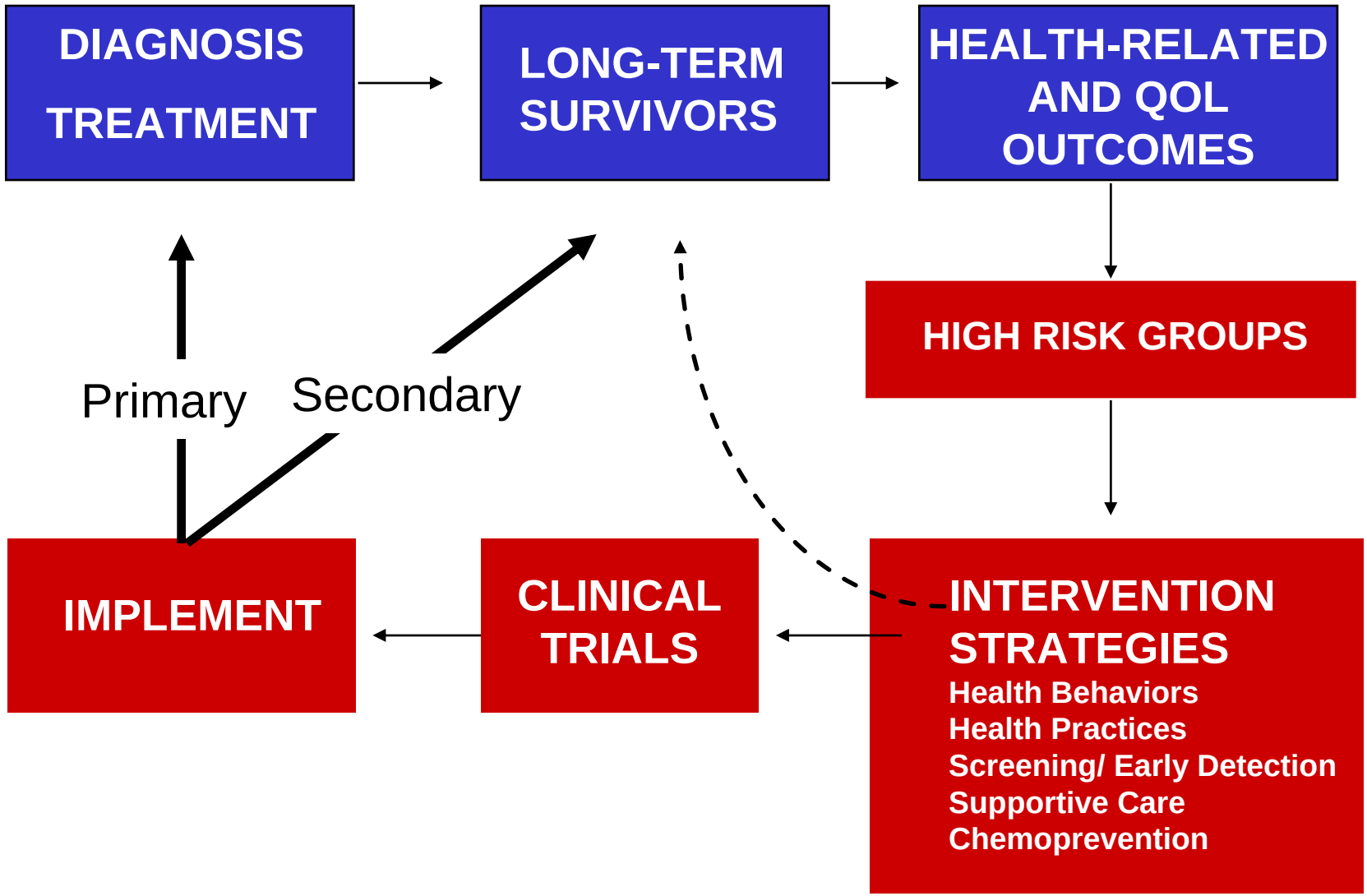
- Therapeutic exposures
- Potential Late Effects
- Risk Factors
- Highest Risk
- Periodic Evaluations
- Recommended Frequency
- Health Protective Counseling
- Considerations for Further Testing
- Cancer Screening
- General Healthcare
- References

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Anti-Tumor Antibiotics								
Bleomycin	23	**Interstitial pneumonitis** **Pulmonary fibrosis**	**Host factors** Younger age at treatment	**Treatment factors** Bleomycin dose ≥ 400 U/m²	Physical exam PFTs	Yearly Baseline upon entry to	**Health Link:** Pulmonary Health Bleomycin Alert	Pulmonary consultation in patients with symptomatic or progressive pulmonary dysfunction
		See related topics: **Chest/thoracic radiation** **Busulfan** **Carmustine** **Lomustine** **Clinician Info Link:** Administration of high concentrations of oxygen may result in chronic progressive pulmonary fibrosis.	**Treatment factors** Higher cumulative dose Combined with other pulmonary toxic therapy: - cyclophosphamide - doxorubicin - busulfan - dactinomycin - carmustine (BCNU) - lomustine (CCNU) - thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **Medical conditions** Renal dysfunction High dose oxygen support such as during general anesthesia **Health behaviors** Smoking	(injury observed in doses 60-100 U/m² in children)	(including DLCO and spirometry) and CXR	long-term follow-up and prior to general anesthesia Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	Avoid SCUBA diving due to potential exacerbation of pulmonary fibrosis with high oxygen concentrations. Notify physicians of health history and risk of worsening fibrosis with high oxygen exposure such as during general anesthesia.	Influenza and Pneumovax immunization.

Issues Relating to Interventions



Issues Relating to Interventions



Opportunities for Cancer Control Research

- Health Behaviors
  - Diet
  - Exercise
  - Tobacco, Alcohol
- Health Practices
  - Health Maintenance
  - Screening
- Supportive Care
  - Endocrinolog
  - Psycho social
- Chemoprevention

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SJCRH
Consortium for Interventional Research

- Identification of 5-7 institutions

- Randomized trials of interventional strategies
- Trials typically consisting of 100-200 subjects
- Approximately 1-2 years of accrual
- Demonstrate feasibility/effectiveness of intervention

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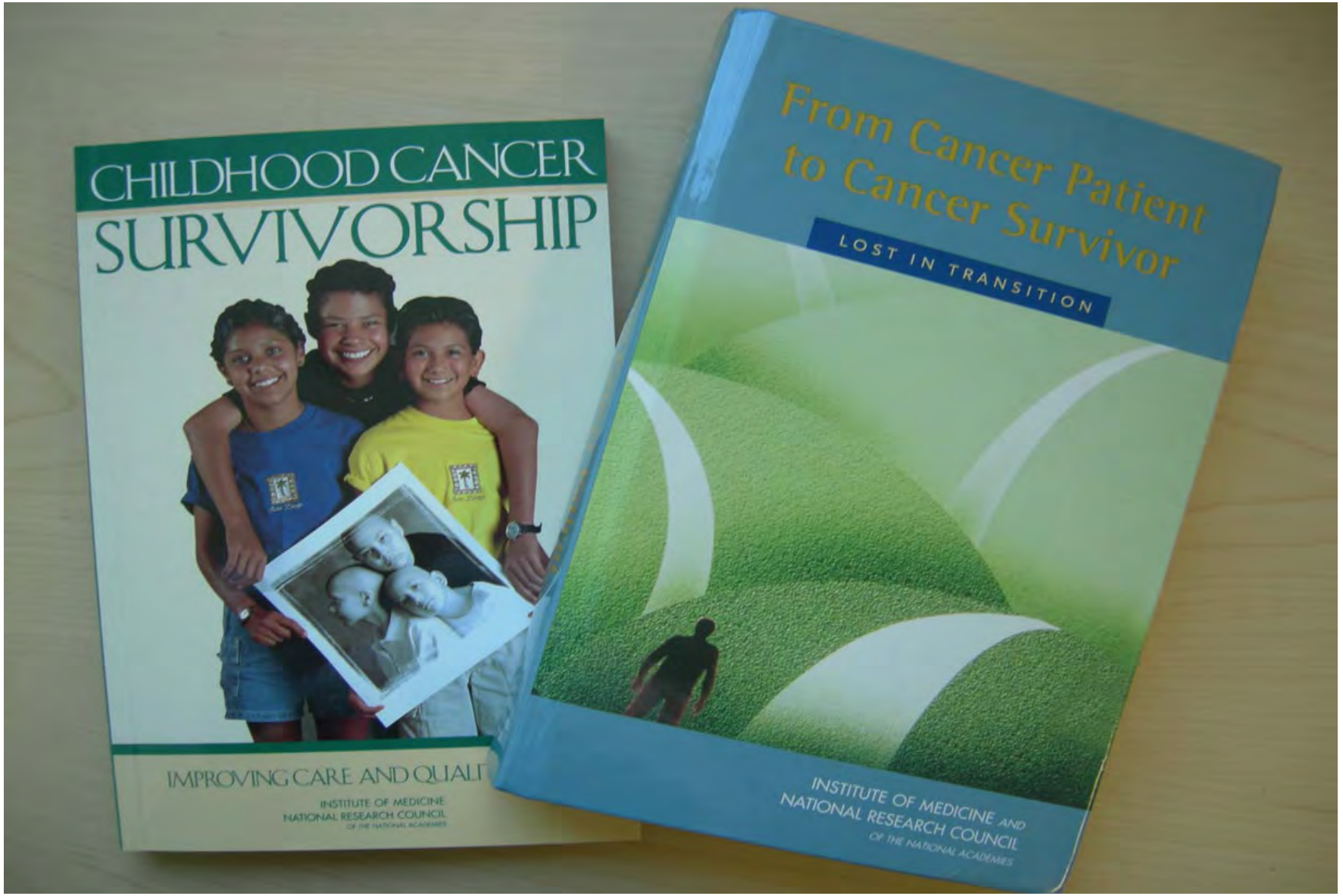
Institute of Medicine Reports



Childhood Cancer Survivor Study

- CCSS is an NCI-funded Resource
- Available to Researchers
- Analysis and Publication of Existing Data
- Use of Biological Samples
- Investigator Initiated Research - Grants
- Interventional Research

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ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Childhood Cancer Survivor Study

www.cancer.umn.edu/ccss